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THE SURGICAL TREATMENT OF ACUTE CHOLECYSTITIS

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THE surgical treatment of acute cholecystitis still remains a controversial subject in some quarters, but as time goes on it is being more and more widely accepted as the policy of choice. Confusion has often arisen from a lack of clarity in defining the basic terms of the policy, particularly "acute cholecystitis" and "surgical treatment." The first, acute cholecystitis, may be best defined as a phase of biliary tract disease manifested by the signs and symptoms of an acutely inflamed or obstructed gall bladder usually, but not always, associated with gallstones. The early surgical treatment of this condition consists of cholecystectomy or cholecystostomy as soon as the patient has been so prepared as to be considered in optimum condition for operation, with no contraindications existing for undertaking either of these procedures.

A total of 697 patients with acute cholecystitis have been operated upon by the surgical service of The New York Hospital—Cornell Medical Center, from September 1, 1932 to September 1, 1949, a period of 17 years. From time to time during this period we have reported our experience (7, 8, 9) with these patients and we have repeatedly advocated the early surgical treatment of acute cholecystitis when the patient is adequately prepared, unless some condition exists that is not immediately reparable and which contraindicates operation. That the trend throughout the United States is in favor of this policy is evident from the growing number of papers (1 to 6, 10) from widely distributed clinics reporting significant case series. These reports invariably emphasize a low incidence of morbidity in postoperative complications as well as a low mortality rate, demonstrating beyond question that operation may be carried out for acute cholecystitis with minimal risk to the patient. Perhaps of equal or even greater importance is the fact that it does much to interrupt the progress of biliary tract disease.

Since the majority of patients with biliary tract disease are women who have had one or more children, it is common to obtain a history of symptoms dating from the early twenties, and since these symptoms so frequently include acute attacks, the advantage of early operation for acute cholecystitis is apparent, not only for the acute stage, but for the chronic phase of the disease as well. The fact that we have not had a death in our group under 40 years of age for a period of 17 years, save for 1 child with acute typhoid cholecystitis, is significant and lends support to the contention that interruption of biliary tract disease can best be accomplished soon after its onset.

In our series of 697 patients, 429 were under 50 and 268 were 50 years of age or over. There was a total of 19 deaths in the group, a mortality rate of 2.7 per cent. The marked difference in the mortality rates of the two age groups, however, is significant. In the older group of 268 patients there were 13 deaths, a mortality of 4.9 per cent, whereas in the younger group of 429 patients there were only 6 deaths, a mortality rate of 1.4 per cent.

From the Department of Surgery, The New York Hospital—Cornell Medical Center.

TABLE I.—SUMMARY OF POSTOPERATIVE DEATHS—PATIENTS UNDER 50 YEARS OF AGE
The New York Hospital—September 1, 1932 to September 1, 1949

	Sex	Age	Biliary disease history (years)	Duration of attack (days)	Jaundice	Findings	Operation	Cause of death
1.	M	41	5	1	+	Acute cholecystitis	Cholecystectomy	Cardiac and renal failure; liver death
2	F	49	15	3	+	Acute cholecystitis	Cholecystectomy	Subdiaphragmatic abscess; peritonitis
3.	F	49	12	2	o	Acute cholecystitis, stones in common duct, acute pancreatitis	Cholecystectomy, choledochotomy	Pulmonary emboli 27th postoperative day (no autopsy)
4.	M	44	4	10	o	Acute cholecystitis	Cholecystectomy	Hypertension, cardiorenal failure
5.	F	49	3	3	o	Acute cholecystitis, cholelithiasis	Cholecystostomy	Coronary occlusion (no autopsy)
6.	M	46	?	3	o	Acute cholecystitis wth gangrene	Cholecystostomy	Hypertensive cardiovascular disease (terminal phase) with necrotizing arteritis and arteriolitis

These figures indicate the desirability of reducing the number of operations in the older group. These are the patients with a higher incidence of complications leading to death from acute cholecystitis if they are not operated upon. The difference between a mortality rate of 4.9 and 1.4 per cent clearly suggests that to operate for acute cholecystitis before the patient reaches the age of 50 will do much to reduce the overall mortality. One would not expect that acute cholecystitis can be prevented after 50, but we believe that it can be materially reduced if those with attacks of acute cholecystitis are operated upon when they first begin to have them, and second, if those who have chronic cholecystitis and cholelithiasis are treated by surgery early in the course of their disease, preferably before the age of forty. If cholecystectomy can be performed for chronic cholecystitis and cholelithiasis with an operative risk of less than 1 per cent fatality, then there can be little justification for the medical, or nonsurgical, management of the disease. Conservative measures only render the disease a little more tolerable to the patient and at the same time permit continuation of the deleterious effects that biliary tract disease may have upon the liver. Indeed, long term studies are urgently needed to throw light on the etiology and pathogenesis of biliary tract disease and its relation to other systemic changes.

The surgical treatment for our 697 patients has been cholecystectomy or cholecystostomy, with choledochotomy added in 61 instances. Six hundred and sixteen patients, or 88.4 per cent of the total number, were treated by cholecystectomy, the procedure of choice. However, for one reason or another, this procedure was deemed inadvisable for the 81 remaining patients, 11.6 per cent, and these patients were subjected to cholecystostomy. Cholecystostomy is a compromise procedure, but at times it should be resorted to without hesitation. When indicated, it may save life by averting immediate disaster, and will tide the patient over for definitive treatment later when it can be accomplished with much less risk. We reserve choledochotomy for those patients with evidence of common duct obstruction. Only 61, or 8.75 per cent, have had this procedure added to cholecystectomy or cholecystostomy. In the entire group of 697 patients, there were 19 deaths, a mortality of 2.7 per cent.

Of the 268 patients 50 years of age and over, 223 or 83.2 per cent were treated by cholecystectomy, and 45 or 16.8 per cent by cholecystostomy. The high incidence of cholecystostomy is indicative of the number of seriously ill patients for whom the more radical procedure of cholecystectomy was deemed inadvisable. Thirty in this group were subjected to choledochotomy, an incidence of 11.2 per cent. Stones were found in 21 cases or 70 per cent of those explored. This is 7.8 per cent of the total. In this group there were 13 deaths, a mortality of 4.9 per cent.

TABLE II.—SUMMARY OF POSTOPERATIVE DEATHS—PATIENTS 50 YEARS OF AGE AND OVER
The New York Hospital—September 1, 1932 to September 1, 1949

	Sex	Age	Biliary disease history (years)	Duration of attack (days)	Jaundice	Findings	Operation	Cause of death
1.	F	66	8+	3	+	Acute cholecystitis with perforation and peritonitis	Cholecystectomy with drainage	Peritonitis
2.	F	67	4+	7	o	Acute cholecystitis with gangrene	Cholecystostomy	Peritonitis, bacteriemia
3.	F	50	20+	10	+	Acute cholecystitis, cholelithiasis, common duct obstruction	Cholecystostomy	Bacteriemia, stone in common duct, thrombosis hepatic artery
4.	M	72	7+	8	+	Acute cholecystitis, cholelithiasis	Cholecystostomy	Hepatic failure, biliary cirrhosis
5.	F	57	?	4	o	Acute cholecystitis, cholelithiasis	Cholecystectomy, drainage abscess	Subhepatic abscess (no autopsy)
6.	F	70	12+	8 hrs.	o	Acute cholecystitis, cholelithiasis	Cholecystectomy	Coronary occlusion, cardiac failure
7.	F	64	2+	2	+	Acute cholecystitis	Cholecystectomy with drainage	Adrenal insufficiency
8.	F	54	4+	3	+	Acute cholecystitis, common duct obstruction	Cholecystectomy, common duct exploration	Leakage from cystic duct, subphrenic abscess, pancreatic necrosis
9.	F	72	?	3	o	Acute cholecystitis carcinoma of cecum	Cholecystectomy, ileocolostomy	Intestinal obstruction, hypertensive cardiac disease
10.	M	69	8	2	+	Acute cholecystitis	Cholecystostomy, peritoneal drainage	Bile peritonitis
11.	F	61	10	5	o	Acute cholecystitis	Cholecystectomy	Anoxia, brain damage, anesthesia
12.	M	71	?	4	+	Acute cholecystitis, cholelithiasis, perforation of gall bladder	Cholecystostomy	Peritonitis, uremia (no autopsy)
13.	F	57	?	4	o	Acute cholecystitis, cholelithiasis	Cholecystectomy	Coronary occlusion (no autopsy)

The incidence of choledochotomy was very much lower in the group of 429 patients under fifty. In 31 cases, or 7.2 per cent, the common duct was explored. Stones were recovered in 19 cases which was 61.3 per cent of those explored, or 4.4 per cent of the total. This is in keeping with our experience in general, namely that the older the patient and the longer the duration of biliary tract disease, the higher is the incidence of stone in the common duct. In a small series of 56 patients followed from 10 to 15 years after cholecystectomy for acute cholecystitis, no evidence of common duct stone has developed.

Of the total number of patients, 429 were under 50 years of age. In this group there were 6 deaths, a mortality rate of 1.4 per cent. Three hundred and ninety, or 90.9 per cent, were treated by cholecystectomy; 39, or 9.1 per cent, by cholecystostomy, and 31, or 7.2 per cent had, in addition, common duct exploration. A review of the deaths in this group reveals that of the 5 upon whom autopsies were performed, 4 showed well advanced cardiovascular disease (Table I). In 1 of these acute cholecystitis seems to have been only a part of the terminal phase of the cardiovascular disease.

Sixty-one patients, or approximately 10 per cent of our total series, were subjected to choledochotomy. In 40, or 66 per cent, stones were recovered. We explore the common duct only on specific indication such as palpable stones within the duct, distention of the duct, a past history of jaundice, or the presence of a marked jaundice. A distinction should be made between a mild degree of jaundice, associated with inflammatory reaction throughout the biliary tract, which is frequently associated with acute cholecystitis, and true common duct obstruction. The incidence of postoperative complications in patients requiring common duct exploration appears higher than when exploration is not necessary. At the

same time it may be said that these patients are usually found in the group that is more seriously ill. For the extremely ill, debilitated, and jaundiced patient, decompression, namely cholecystostomy, may be used as an emergency compromise procedure, with exploration of the common duct to follow when the patient is in a much more improved condition. The presence of jaundice requires determination of the blood prothrombin time and evaluation of any bleeding tendency, but in the presence of an acute episode time may not permit this. Therefore, the use of whole blood transfusions and parenteral administration of vitamin K may prevent serious postoperative hemorrhage in such patients. Because this same group of patients often have liver damage, special consideration should be accorded them as indicated.

A summary of our postoperative deaths follows. Thirteen of the 19 deaths were of patients 50 years of age or older. The majority of these had given a long history of biliary tract disease. In fact, the two most common causes of death were infection arising from the biliary tract and some complication of cardiovascular disease. It is reiterated here for emphasis that earlier operation might have reduced this mortality—operation years earlier to rectify the condition of biliary tract disease itself, and operation days earlier in the case of an acute attack.

Over the past 40 years the population of the United States has shown a greater proportional increase in the number of people over 50 years of age. In 1940 the census showed that 20.4 per cent of our population was over 50. It is now believed that by 1950, 25 per cent will be in this age group. Therefore our figures which show an increasing mortality rate in the group over 50 become of greater importance (Table II). As previously pointed out, the mortality rate associated with operation in this group parallels the higher mortality rate in this group that is the result of complications from acute cholecystitis not treated by surgery. Therefore, to reduce the number of patients over 50 requiring operation, when the risk is much greater, a direct attack upon biliary tract disease before the patient reaches this age is logical.

Of the 6 remaining deaths occurring in our group under 50, one was directly the result of infection from the acute cholecystitis, 1 was from a pulmonary embolus, and the 4 remaining were associated with previously recognized and well advanced cardiovascular disease. In 2 of the latter it was evident before operation that the cardiovascular disease was in its terminal phase, and it may be said that acute cholecystitis developed during the terminal phase and was a part of it. In each case, a palpable gall bladder was evident in a typical clinical picture of acute cholecystitis. Cholecystostomy was performed under local anesthesia to decompress the biliary tract. We feel that this prevented perforation in 1 patient whose gall bladder was gangrenous at the fundus. A brief summary is presented to emphasize that acute cholecystitis may be a part of terminal cardiovascular disease.

A 46 year old, white, married butcher was admitted to the medical service of The New York Hospital on January 14, 1947, for the treatment of hypertension. For 6 months he had had blurring of vision, dyspnea on exertion, early fatigue, general malaise, nocturia, anorexia, and a 35 pound weight loss. He was a chronically ill individual suffering from well advanced hypertensive cardiovascular disease. He had cardiac enlargement, marked changes in the vessels of the fundi, and his blood pressure was 240/140. The urine contained albumin and red and white cells and had a low specific gravity. On admission his blood urea nitrogen was 19, but rapidly increased until it reached 61 four days later. The patient then developed acute cholecystitis accompanied by a high leucocytosis. Because of progressive manifestations of this complication he was transferred to the surgical service for operation. Under local anesthesia the gall bladder was exposed. The entire fundus was found to be gangrenous, but no stones were found. A cholecystostomy was done, but the patient did not improve. His blood urea nitrogen continued to rise and on the 5th day after operation he died in uremia. His blood urea nitrogen was then 91.

Postmortem examination revealed the classical findings of hypertensive cardiovascular disease, with disseminated necrotizing arteritis and arteriolitis. There was marked involvement of the heart and kidneys. The biliary tract contained no stones. Microscopic examination of the gall bladder revealed necrotizing changes in most of the arteries, some of which showed thrombi beginning to organize. There were areas of hemorrhage and polymorphonuclear exudate and coagulation necrosis.

Perforation of the gall bladder with biliary peritonitis may have been the immediate

cause of death in the group of terminal cardiovascular cases. However, we have performed cholecystostomy in similar situations with survival. Whether or not to operate on such patients is determined by the clinical judgment of those caring for the patient. In the case just summarized we do not believe that the cholecystostomy done under local anesthesia was a contributing cause of death. We believe death was impending, and that had the cardiovascular disease not been in its terminal phase, the operation would have accomplished its purpose. We must admit, however, that by the same reasoning one might assume that if the degree of arteritis and arteriolitis was not sufficient to cause death, perforation of the gall bladder and resulting bile peritonitis might not result.

Operation under such circumstances is hazardous, but equally hazardous, we believe, is withholding operation. A patient with far advanced cardiovascular disease is as likely to die from renal failure as from a complication of acute cholecystitis.

The complications of acute cholecystitis are admittedly much fewer in the younger group. As a result, these individuals tend to postpone treatment and believe themselves justified in tolerating their symptoms. This, however, only permits disease of the biliary tract to progress over the years. In a recent review of 56 patients whom we followed for 10 years or more after early operation for acute cholecystitis, we found only 4 who had had any residual symptoms referable to the biliary tract. This is admittedly a very small series and we can only suggest that more such studies would contribute materially to our knowledge of how best to interrupt biliary tract disease.

DISCUSSION

Acute cholecystitis constitutes a problem of varying importance and urgency, depending on whether or not it occurs as an early phase of biliary tract disease in a young woman recently pregnant, for example, or as an episode in the later stages of chronic biliary tract disease, as with men and women in the older age group, or as a complication of a terminal systemic disease, or following some operative procedure unrelated to the biliary tract. As to the first, acute cholecystitis in the young, recently pregnant woman, the postoperative morbidity of complications and the mortality rate are minimal and the complications of perforation and peritonitis are infrequent. We believe that operation is the best method for interrupting biliary tract disease and that the patient should be subjected to early surgical treatment. For those in a slightly older age group but still under 50, both women who have not been pregnant and men, acute cholecystitis appears to be a somewhat more severe process. Complications under nonsurgical treatment are more likely to occur, but this group will tolerate operation almost as well as the first unless they are suffering from some systemic involvement such as cardiovascular disease, diabetes, or renal impairment. A third group consists of those over 50, the majority with a long history of biliary tract disease. The older the patient and the longer the duration of biliary tract disease, the more common are the complications of acute cholecystitis if not treated by surgery. By and large, the older the patient the more difficult it is to estimate the exact nature of the process by physical examination, temperature, or white blood count, namely, whether the wall of the gall bladder is gangrenous, or whether perforation is impending. Furthermore, the incidence of common duct stone is greater in the older group. These patients are also more prone to develop postoperative complications that contribute to a higher mortality rate. Here again, however, early surgical treatment is the best protection for the patient.

In a final group are those patients who develop acute cholecystitis as a complication of the terminal phase of a systemic disease, such as cardiovascular disease with a marked arteritis and arteriolitis. Whether or not operation is justified for such patients depends chiefly on the probable expectancy of life at the time. Since this is extremely difficult to estimate, and since catastrophic perforation of the gall bladder with resulting bile peritonitis can be averted by cholecystostomy under local anesthesia, surgery to us seems indicated. When acute cholecystitis develops as a complication following operation for conditions unrelated to the biliary tract, the problem is primarily

one of diagnosis and the type of surgical treatment is dependent upon the local process and the patient's general condition.

SUMMARY

A series of 697 patients with acute cholecystitis treated surgically is reported. Of the 429 patients under 50 years of age, 390 or 90.9 per cent were treated by cholecystectomy and 39 or 9.1 per cent by cholecystostomy. In addition, 31 or 7.2 per cent were subjected to common duct exploration. The mortality rate for this group was 1.4 per cent. In the older age group, those 50 and over, there were 268 patients and among them the more difficult clinical problems. In this group, only 223 or 83.2 per cent were treated by cholecystectomy, whereas cholecystostomy was done for 45 or 16.8 per cent. In addition, 30 or 11.2 per cent had exploration of the common duct. The mortality rate for this older group was 4.9 per cent, or three times that of the younger group.

It is contended that surgical treatment during the early phase of cholecystitis, whether it be acute or chronic, is the best means of interrupting biliary tract disease.

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THE EFFECT OF EPINEPHRINE AND NOREPINEPHRINE ON THE CONTRACTIONS OF THE HUMAN UTERUS IN LABOR

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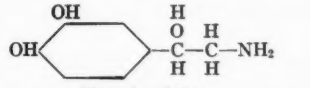
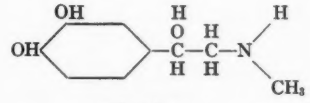
THE effect of adrenalin on the pregnant human uterus has been extensively studied in the past 25 years. Recently, it has been demonstrated that the extracts of adrenal medulla in clinical use are actually a mixture of l-epinephrine and l-norepinephrine.[1] These two hormones have distinct and in some respects different influences on the dynamics of the human circulation. They also have distinct and opposite effects on the activity of the intact pregnant human uterus.

Levoepinephrine has long been available in purified form, but it was not until 1948 that pure l-norepinephrine became available, after the successful resolution of racemic (dl-) norepinephrine into its two separate forms. The chemical difference between the two hormones of the adrenal medulla is slight. As may be seen in the structural formulas epinephrine contains a methyl group that is absent from norepinephrine. Physiologically, major differences between the two drugs have already been observed in their influence on the human circulation. When administered in minute amounts by intravenous drip, l-epinephrine causes elevation of systolic blood pressure, tachycardia, over-all vasodilatation and increased cardiac output. When similarly given, l-norepinephrine causes elevation of systolic and diastolic pressures, bradycardia, over-all vasoconstriction but no definite change in cardiac output.



Norepinephrine
(3, 4-dihydroxyphenylethanolamine)



Epinephrine
(3, 4-dihydroxyphenylethanolmethylamine)

The effects of these two hormones on the pregnant human uterus are also quite different. Levoepinephrine, like adrenalin, causes a transitory decrease in uterine activity and uterine tone. Levonorepinephrine on the other hand causes a marked and persistent increase in the frequency of uterine contractions and a transitory rise in uterine tone.

MATERIALS AND METHODS

The present studies were made on obstetric clinic patients of the Sinai Hospital of Baltimore. The patients were obstetrically normal and in active labor at term. Analgesia for labor consisted of either barbiturate-demerol-scopolamine mixtures or continuous catheter caudal conduction block. Postpartum observation disclosed no evidence of deleterious effects of the experimental drugs in either the mothers or the infants.

Uterine recordings were made with the Reynolds multiple channel tokodynamometer (11). The principal advantages of this device are two. The sensitive elements are externally placed and therefore themselves do not stimulate uterine activity. The tokodynamometer provides simultaneous recordings from several areas on the anterior wall of the uterus, thereby yielding information concerning the coordination of uterine activity.

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[1] A multiplicity of names for these drugs has developed. Epinephrine is known also as adrenaline, adrenin, and suprarenin; norepinephrine as noradrenaline, arterenol, and levophen. For purposes of clarity, the term l-epinephrine will be employed here to refer to the pure levorotatory form of 3, 4-dihydroxyphenylethanolmethylamine and the term l-norepinephrine for pure levorotatory 3, 4-dihydroxyphenylethanolamine. The term adrenalin will be used for the extract of beef adrenal glands, marketed for medicinal use under that name, which has now been shown to consist of a mixture of these two substances.

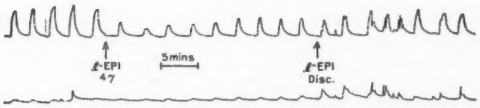

Fig. 1. Uterine recording of a 31 year old multipara in active labor under caudal analgesia. The upper tracing is from the fundus uteri, the lower from the junction of fundus and lower uterine segment. At the left the patient was 4 centimeters dilated, at the right 8 centimeters, with the vertex at 2 centimeters below the spines. At the first arrow, an intravenous drip of l-epinephrine was begun at a rate of 4 micrograms per minute. At the second arrow this was discontinued. The effects described in the text are all present.

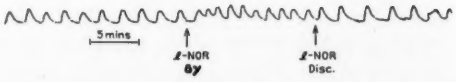

Fig. 2. Uterine recording of a 20 year old primipara in the second stage of labor under caudal analgesia. The single lead reproduced is a tracing from the fundus uteri. An intravenous drip of l-norepinephrine was begun at the first arrow at a rate of 8 micrograms per minute, and discontinued at the second arrow. The blood pressure changed from 100/80 to 160/110 and the pulse from 80 to 52. Increase in frequency of contractions and a transitory tone rise can be seen. .

The stock solution of l-norepinephrine employed contained l-norepinephrine bitartrate, with small amounts of chlorbutanol, sodium bisulfite, and sodium chloride, 1 cubic centimeter of solution equaling 1 milligram of free l-norepinephrine base. The l-epinephrine employed was in an identical solution.[1] For experimental use, 0.5 cubic centimeter of one of the stock solutions was added to a standard 500 cubic centimeter flask of either 5 per cent glucose in distilled water or normal saline solution. This flask and an identical one without drug were then fitted with intravenous drip sets calibrated to deliver 10 drops per cubic centimeter. These sets were connected with a three-way stopcock and the latter fitted with a 20 gauge needle. The rates of flow were adjusted to the desired initial rates and the needle then placed in an arm vein with the control solution running. The control solution and the experimental solution could be alternated or their individual rates of flow adjusted without awareness on the part of the patient. Blood pressure and pulse were determined at least every 5 minutes in most experiments and the fetal heart rate counted as frequently as feasible.

RESULTS

Levoepinephrine. Six patients in active labor were given 4 micrograms of l-epinephrine per minute by intravenous drip.[2] Two were receiving systemic sedation and 4 continuous caudal analgesia. The effects noted were the same as those already reported with adrenalin under the same circumstances.

[1]All dosages are stated in terms of the weight of the active base itself.

[2]This is equivalent to 0.06 minim of the undiluted stock solution per minute.

These effects may be summarized as follows (10):

1. Inhibition of uterine activity even in the absence of changes in blood pressure or pulse rate and without the appearance of tremulousness. This inhibition appears promptly after the start of the intravenous drip and has the following characteristics: (a) diminution or disappearance of uterine contractions throughout the uterus; (b) decrease in uterine tone; (c) increase and inequality in the length of the interval between uterine contractions.

2. During administration of the drug at a constant rate there is partial recovery from inhibition, usually about 15 minutes after the start of the intravenous drip.

3. After discontinuance of the drip, uterine activity returns promptly to its predrip levels, and a few minutes later this is followed by an increase in tone, force, and frequency of contractions above the predrip levels, which lasts about 5 minutes.

As has been noted in the study of adrenalin, these effects are not seen in every patient. In the present group they were present in 5 of the 6 patients.

Levonorepinephrine. Ten patients in active labor were given l-norepinephrine by intravenous drip at rates varying from 2 to 10 micrograms per minute.[3] Six were receiving

[3]Since the use of l-norepinephrine in pregnant women has not been previously reported, the drug was given by intravenous drip to 6 puerperal women before its administration to patients in labor. The responses of blood pressure and pulse to 2 to 10 micrograms per minute, or approximately 0.03 to 0.17 microgram per kilogram per minute are of the same type as those reported in males. The response of blood pressure and pulse in this small group of pregnant and puerperal women appeared to be somewhat greater than that reported for the same doses in males, however. None of these patients noted any subjective changes except for an increase in the frequency and severity of afterpains in 4 of the puerperal patients, and an ill defined swelling of the neck, possibly due to thyroid engorgement, in 1 patient. These complaints disappeared with discontinuation of the hormone.

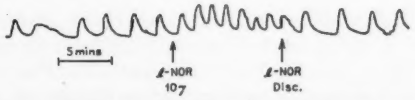

Fig. 3. Uterine recording of a 23 year old nullipara in the second stage of labor under caudal analgesia. The single lead reproduced is from the fundus uteri. Intravenous drip of 10 micrograms of l-norepinephrine per minute was given as indicated by the arrows. Blood pressure changed from 110/80 to 140/95. The effect on the uterine contractions is striking.

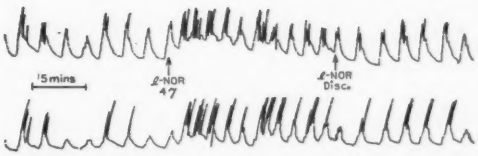

Fig. 4. Uterine recording of a 35 year old multipara in active labor under sedation with nembutal, demerol, and scopolamine. The upper lead is from the dome of the fundus uteri, the lower about 2 centimeters above the umbilicus. Intravenous drip of l-norepinephrine at a rate of 4 micrograms per minute was given as indicated by the arrows. The patient reached full cervical dilatation just after the drip was begun. The striking effect of the l-norepinephrine in both leads is clear.

continuous caudal analgesia and 4 systemic sedation.

In 9 patients a definite increase in the frequency of uterine contractions occurred immediately after the start of the intravenous drip of l-norepinephrine. This increase persisted as long as the dose was maintained. In the other patient, whose uterine activity at the time of the experiment was not the rhythmical type characteristic of normal progressive labor, no distinct effect was noted. Increases in the rate of administration were regularly accompanied by further increases in the frequency of contractions until in 1 case contractions were occurring at least once a minute. Uterine tetany was not produced by any of the doses used. The effect of a rate of 8 micrograms on frequency per minute was the same whether it was arrived at gradually through steps of 2, 4, and 6 micrograms per minute or whether the 8 micrograms were given initially.

Immediately after the administration of l-norepinephrine was begun there was often a transitory rise in uterine tone which was less striking with succeeding increases in dose.

Despite the increase in frequency of contractions, there did not appear to be an increase in the force or a change in the contraction pattern of individual contractions of the fundus uteri. In a few instances there was a marked increase in the contractile activity of the lower portion of the fundus during the l-norepinephrine drip, which represents an unfavorable alteration of the gradient of force of uterine contraction. However, in at least 1 case, activity in the lower portion of the fundus decreased. In every instance discontinuance of the drip resulted in an immediate return to the type of activity present prior to the administration of l-norepinephrine, except for 1 patient who almost had a precipitate delivery a few minutes after the drip was started.

Despite the total absence of symptoms, the effects on blood pressure and pulse were quite marked. At 2 micrograms per minute little change was noted, but 8 and 10 micrograms induced a change in blood pressure from 100/70 to 170/110 millimeters of mercury and in pulse from 80 to 50 beats per minute in some instances. Despite changes of this magnitude and an accompanying increase in the frequency of uterine contractions, no effect on the fetal heart rate or fetal condition was noted. As stated previously, no deleterious effects in mother or infant could be detected after delivery.

There was no clear-cut evidence of the effect of l-norepinephrine on the course of labor, largely because the drug was never given over a prolonged period of time. There was no indication that it slowed labor, however, and as noted above 1 patient virtually precipitated shortly after the drug was begun.

DISCUSSION

The effect of adrenalin on the pregnant human uterus[1] has been a matter of interest ever since Rucker in 1925 first observed that the hormone causes diminution of uterine activity. A long series of papers has appeared since Rucker's publication, reporting adrenalin employed in widely varying doses by many

[1]The first observation of the oxytocic effect of adrenalin on the pregnant human uterus was that of Neu, *Gyn. Rund.*, 1907, 1:509-511, who employed a large dose and noted its effect at cesarean section.

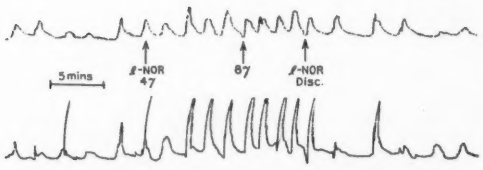

Fig. 5. Uterine recording of a 27 year old multipara in active labor under sedation with seconal, demerol, and scopolamine. The upper lead is from the dome of the fundus uteri, the lower at the umbilicus. The patient was approximately 7 centimeters dilated during the period of the recording. Intravenous drip of l-norepinephrine at a rate of 4 micrograms per minute was begun at the first arrow and then increased to 8 micrograms per minute as indicated. The appearance of large contractions in the lower lead after initiation of norepinephrine may be noted. There is a further increase in frequency when the rate of administration of the hormone is doubled.

routes of administration, both clinically and under various experimental circumstances. No consistent opinion concerning the effect of adrenalin has emerged from these investigations.

Recently, Kaiser and Harris have published a review of previous work on adrenalin and an extensive reinvestigation of its effect on the pregnant uterus both during pregnancy and in labor, using the Reynolds multiple channel tokodynamometer (10). They took occasion in discussing their results to comment on the possible role of adrenalin and the sympathetic nervous system in normal and abnormal labor. The present study is a further investigation of this matter, employing identical techniques.

For 40 years, it has been suggested that epinephrine might not be the effector substance of the sympathetic nervous system (3). For 15 years it has been further suggested that norepinephrine, the demethylated form of epinephrine, might be this substance (1). Not until the resolution in 1948 of the physiologically active levorotatory isomer from racemic norepinephrine was it possible to test these hypotheses adequately (14). Since that time a series of studies on the effects of epinephrine and norepinephrine on the human circulation have appeared (2, 5, 7, 13). These demonstrate that epinephrine in minute doses is responsible for an increase in blood pressure, most particularly in its systolic levels, for an increase in cardiac output, for over-all dilatation of the vascular bed, and for an increase in pulse rate. Norepinephrine, on the other hand, increases the systolic and diastolic pressures proportionally, has little or no effect on cardiac output, causes an over-all constriction of the vascular bed, and slows the pulse rate markedly. This last effect can be in part inhibited by atropine. There is some evidence that the two substances when given simultaneously are antagonists for some of their actions.

These observations acquire more significance in the light of the demonstration that U.S.P. adrenalin, an extract of adrenal of cattle, may contain appreciable amounts of norepinephrine, of the order of magnitude of 12 to 36 per cent (6, 15). Pheochromocytomas of the human adrenal have been shown to contain as much as 90 per cent norepinephrine (6, 8), and, indeed normal human adrenal medulla unquestionably secretes norepinephrine as well as epinephrine under some physiological conditions (4). Students of this field, acknowledging that some of the effects of sympathetic nervous system activity are manifested by each substance, have suggested that the concept of an effector sympathin (E) be altered to allow for epinephrine as sympathin A and norepinephrine as sympathin N (5).

In regard to their effect upon smooth muscle activity, the matter is still more complicated. In every smooth muscle viscus on which the two hormones have been tested, norepinephrine has been inhibitory where epinephrine has been inhibitory, and excitatory where epinephrine is excitatory. This is clearly not true of the intact pregnant human uterus (9).

It has been pointed out that if subsequent studies demonstrate that the relative proportions of epinephrine and norepinephrine in adrenal secretions are maintained under all conditions of adrenal stimulation, no fundamental revision of our present concepts of mediation of sympathetic nervous system activity is required. If, however, varying conditions call forth varying proportions of the two substances, then our concepts must be revised in terms of the special concentrations of the two hormones in particular circumstances.

Until this can be clarified, it is mandatory that physiological studies be carried out with

the pure substances or with artificially produced mixtures. It is also important in studying these substances to avoid stimulation of the patient's endogenous adrenal secretion. For that reason, some form of analgesia is desirable. Further, since these substances are highly effective in minute amounts and vary from subject to subject in their effect at a given dose level, administration of dilute solutions by intravenous drip is the method of choice and has been employed in the present report as well as in the circulatory studies. This method also avoids the uncertainties of absorption of these substances, which have local effects on blood vessels, from intramuscular or subcutaneous sites of injection.

The mode of action of these hormones on the uterus is not clear. Since both produce hypertension, this can be excluded as the mediator of their opposite uterine effects. While it is known that one is an over-all vasodilator and the other a vasoconstrictor, there is no information as to their effects on the uterine arteries and arterioles, which might conceivably mediate the uterine effects. As Kaiser and Harris pointed out in the case of adrenalin, in parallel experiments under nerve conduction block, the site of action can be localized to: (1) motor nerves which may not be completely blocked; (2) sensory nerves cephalad to the 9th dorsal; (3) sensory nerves beyond the conduction block, including intrinsic nerves of uterus; (4) the myometrium.

Since the effects of adrenalin and l-epinephrine are identical, it appears that the concentration of l-norepinephrine in adrenal extracts in common clinical use is not sufficiently great to alter the effect of the l-epinephrine. It should also be noted that the rebound from adrenalin effect was also found with l-epinephrine. This phenomenon, which is characterized by a rise in uterine tone and an increase in the force and frequency of uterine contractions, has many similarities to the initial effect of norepinephrine. Whether prolonged periods of epinephrine administration induce an increased rate of endogenous secretion of norepinephrine, which might account for the recovery of the uterus from adrenalin inhibition and for the rebound when epinephrine administration is abruptly halted, cannot be decided on the basis of the present information At least in so far as uterine effects are concerned, there is no evidence of any mechanism for recovery from norepinephrine.

Despite marked maternal bradycardia during the higher rates of administration of norepinephrine, no change in fetal heart rate was observed. Since it appears that the bradycardia is a vagal effect, it may be that the absence of a functioning carotid sinus mechanism in the term infant renders it relatively resistant to norepinephrine.

The physiological effects of norepinephrine make it an ideal drug for the treatment of both surgical and anesthetic shock. Early reports of its use for this purpose have been very encouraging (5). In a case of shock due to drug sensitivity in a patient in labor in this hospital, a l-norepinephrine intravenous drip maintained normal blood pressure after the failure of intravenous fluid administration and intravenous ephedrine to do so. Norepinephrine should nevertheless be employed with great caution in shocked pregnant women because its excitatory effect on the uterus may further embarrass the fetal circulation.

Whether norepinephrine accelerates, slows, or has no influence on the course of labor cannot be decided by the present experiments. In a few cases it was responsible for change in the gradient of force in uterine activity both favorable and unfavorable for progressive labor. It has not been used in cases of uterine inertia.

Kaiser and Harris pointed out, in their discussion of adrenalin effects, that: "in difficult labor there is a state of emotional stress which may well induce excessive secretion of endogenous adrenalin. The disorganization of patterns of uterine activity observed in inertial labor resembles in many respects that induced, for brief periods, by exogenous adrenalin."

The role of epinephrine and norepinephrine in these relationships can be established only by meticulous studies of their individual concentrations in the blood in the presence of normal and abnormal labor. Until suitable techniques for these determinations become available, additional information can be expected from further study of uterine responses of excised muscle strips in vitro and of the intact uterus in adrenalectomized animals.

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THE EFFECT OF ADRENERGIC BLOCKADE WITH A BENZODIOXANE DERIVATIVE, 933F, ON HYPERTENSION OF TOXEMIA OF PREGNANCY

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PREVIOUS studies have suggested the possibility that toxemic hypertension might be caused by humoral agents, neurogenic impulses playing a minor role. This was demonstrated by using autonomic blocking agents such as tetraethylammonium chloride, high selective spinal anesthesia, and other nonspecific methods (1, 2, 3, 5, 7, 9, 12). Autonomic blockade with either tetraethylammonium chloride or high selective spinal anesthesia resulted in a negligible fall of blood pressure in toxemia of pregnancy. This led to the belief that in this disease, blood pressure elevation is maintained principally by humoral mechanisms together with intrinsic factors inherent in the vessel walls. As yet, such humoral agents have not been identified.

This study was undertaken to evaluate a possible role of circulating sympathomimetic agents, such as epinephrine, in the genesis of toxemic hypertension using the adrenergic blocking property of a benzodioxane derivative, piperidylmethyl benzodioxane (933F). In man, this drug has been shown to be almost specific against hypertension caused by excessive circulating epinephrine such as that seen in cases of pheochromocytoma (10).

MATERIAL AND METHODS

The material for this study comprised 5 normal term pregnancies, 4 patients with severe pre-eclampsia and 1 with convulsive eclampsia superimposed on pre-existing essential hypertension, submitted to a total of 19 tests. The diagnosis of pre-eclampsia was based on the presence of proteinuria, edema, and hypertension during the last trimester of pregnancy. The age of the patients varied from 17 to 32 years. All of the patients were admitted to the hospital before labor and kept at bed rest without medication for a period varying from 10 to 24 hours. The studies were performed on all patients in the prepartum and postpartum periods. Prepartum responses of normal pregnancies were recorded as near term as possible. In the postpartum period the same patients were tested again, in every case between 48 and 72 hours following delivery.

933F dosage was calculated in terms of body surface, by means of the Dubois body surface chart which is employed in calculating basal metabolic rate. Ten milligrams of the drug were given per square meter of body surface according to the method devised by Goldenberg, Snyder, and Aranow.

All studies were conducted with the patient in the supine position. A control period varying from 5 to 7 minutes, during which the blood pressure was recorded (sphygmomanometer) every minute, was obtained. Then the calculated dose of 933F was given in a rapid intravenous injection in an antecubital vein. Following the injection, the blood pressure was recorded at half minute intervals for 5 minutes and at 1 minute intervals for an additional 5 to 10 minutes. Pulse rate was also recorded. The lowest point to which the blood pressure descended in the first 5 minutes following injection was termed "benzodioxane floor."

RESULTS

Normal term pregnancy. The results are shown in Table I and Figures 1 and 2. Benzodioxane produced very little fall in the blood pressure of normal pregnancy at term. In the prepartum period the mean control blood pressure for the group was 120/74 millimeters of mercury, and the mean benzodioxane floor

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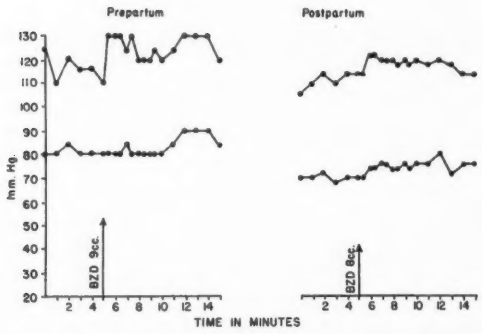

Fig. 1. Individual example of a primipara, A.D., normal term pregnancy, not in labor, tested in the prepartum and postpartum periods with 933F. The slight rise in the blood pressure was possibly caused by emotional reaction to the injection rather than specific action of benzodioxane.

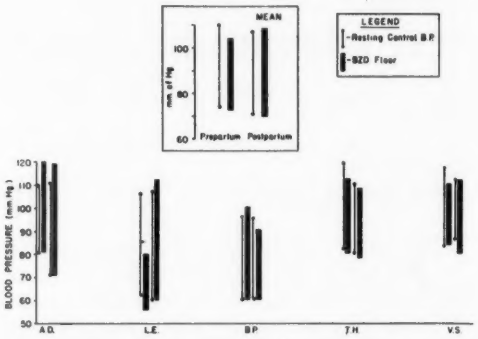

Fig. 2. Benzodioxane "floor" in normal pregnancy. The thin line represents the arithmetic mean of 5 to 6 readings of blood pressure control. The heavy line represents the lowest point to which the blood pressure fell after the injection of the drug. In each line the upper end represents the systolic and the lower end the diastolic blood pressure. In each case, the first part to the left represents the prepartum test while the other represents the postpartum test. In the upper inset is shown the mean blood pressure control and response for the whole normal pregnant group.

was 104/73. In the postpartum period the mean control blood pressure was 104/71 millimeters of mercury and the mean benzodioxane floor was 108/70 millimeters of mercury.

Toxemia of pregnancy. The results are shown in Table I and Figures 3 and 4. Benzodioxane also produced very little or no fall in the blood pressure of pre-eclamptic patients. The mean prepartum control blood pressure for the group was 147/101 millimeters of mercury and the mean benzodioxane floor was 143/100 millimeters of mercury. The mean postpartum control blood pressure was 137/96 millimeters of mercury and the mean benzodioxane floor was 138/94 millimeters of mercury.

There was no change in the pulse rate of either group of patients. In the doses employed side effects were not observed.

TABLE I.—DATA ON CONTROL BLOOD PRESSURE AND BENZODIOXANE "FLOORS" IN THE PREPARTUM AND POSTPARTUM PERIODS OF NORMAL AND TOXEMIC PREGNANCY

Normal term pregnancy	Prepartum		Postpartum	
	Mean control blood pressure	Benzodioxane "floor"	Mean control blood pressure	Benzodioxane "floor"
1. A. D.	110/81	120/81	111/71	119/71
2. L. E.	106/62	80/51	107/60	112/60
3. B. P.	96/60	100/60	95/60	90/60
4. T. H.	119/82	112/80	110/80	108/78
5. U. S.	117/83	110/84	112/86	112/80
Toxemia of pregnancy				
1. A. M.	144/92	138/88	138/86	136/82
2. R. W.	152/98	150/93		
3. E. F.	137/102	130/100	130/95	128/96
4. E. S.	126/94	130/100	119/91	120/88
5. G. H.	175/118	168/118	163/112	170/110

DISCUSSION

In recent years the pharmacologic action of benzodioxane derivatives has been intensively studied in man and animal. As stated in a recent review (14), some members of the benzodioxane series, such as 933F, are predominantly effective against circulating sympathomimetic agents, while others, such as 883F, are effective against both circulating agents and sympathetic nerve activity. It is not the scope of this paper to discuss all the pharmacologic aspects of the benzodioxane derivatives, but it is well to emphasize that in animals, in doses ranging from 0.25 to 2 milligrams per kilogram of body weight, 933F acts specifically against circulating epinephrine. Higher doses which are close to lethal dose limit may depress sympathetic nerve activity (10, 11, 14). Goldenberg and his co-workers have standardized a dose and technique

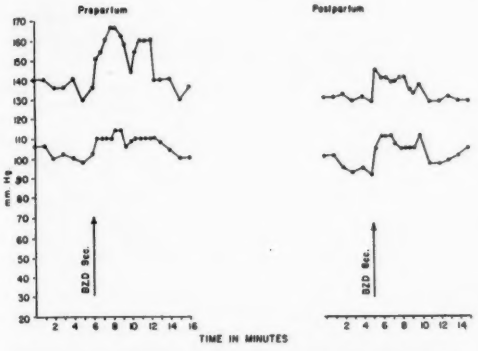

Fig. 3. Individual example of a severe pre-eclamptic patient, E. F., primipara, submitted to 933F in the prepartum and postpartum periods. Here, again, the rise after the injection was considered unsignificant.

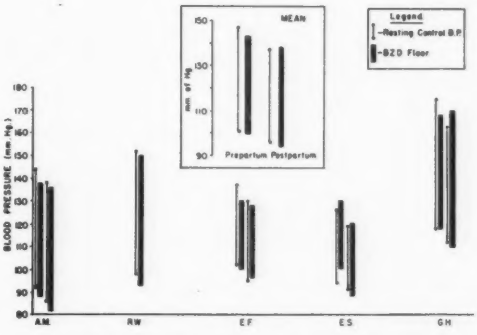

Fig. 4. Benzodioxane "floor" in toxemic pregnancy. There was no significant change in the blood pressure after administration of the drug. (For explanation of the legend see caption of Fig. 2).

whereby the drug is used effectively in the diagnosis of pheochromocytoma. In this disease and by this technique, the drug produces a sharp and marked fall in the blood pressure which lasts for approximately 10 minutes. Further studies (6, 8, 16) have confirmed their findings and at present, the benzodioxane test is considered among the most accurate physiologic tests used in the diagnosis of pheochromocytoma. The drug is not effective against essential hypertension in man (10) or against renal hypertension experimentally induced in animals (4, 11).

The apparent similarity between some of the symptoms of pheochromocytoma and toxemia suggested to us the possibility that both diseases might be due to a common etiologic factor. In both diseases, there is paroxysmal or progressive hypertension, headache, dizziness, epigastric pain, nausea and vomiting.

Also, autonomic blockade with tetraethylammonium chloride produces an abrupt rise in the blood pressure in cases of pheochromocytoma (13). Similarly, in severe cases of eclampsia and pre-eclampsia autonomic blockade with either tetraethylammonium chloride or high selective spinal anesthesia evokes either a rise or no change in blood pressure (1, 3, 5). Thus, it is quite natural that such similarity in symptoms and physiologic tests may lead to the belief that a common factor may be operating in the genesis of hypertension in both illnesses.

Unfortunately, this was not corroborated by this study. As the figures show, there was no fall in the blood pressure of either toxemic or normal pregnancy submitted to 933F. The drug also failed to produce any change in the pulse rate in both groups of patients. To further substantiate the results obtained with 933F, some of the patients were submitted to the histamine test of Roth and Kvale which has also proved to be valuable in the diagnosis of pheochromocytoma. The histamine test also produced no change in the blood pressure of toxemic patients. Thus, on the basis of these results, toxemia of pregnancy and pheochromocytoma are not caused by a common etiologic factor and circulating epinephrine plays no role in the genesis of toxemic hypertension. As a corollary, 933F is of no value in the treatment of toxemia of pregnancy.

SUMMARY

1. A comparative study has been made of the 933F blood pressure responses in the prepartum and postpartum periods of normal term pregnancy and toxemia of pregnancy.

2. There was no fall in the blood pressure in either normal or toxemic pregnancy with 933F administration.

3. Circulating adrenaline plays no role in the maintenance of blood pressure in either normal term or toxemic pregnancy.

4. 933F is of no value in the treatment of toxemic hypertension.

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THE USE OF METHOXAMINE FOR MAINTENANCE OF THE CIRCULATION DURING SPINAL ANESTHESIA

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A SYSTEMATIC study of a series of beta-2-5-dimethoxyphenylalkyl amine compounds resulted in the discovery of methoxamine [β- (2, 5-dimethoxyphenyl)— β - hydroxyisopropylamine HCl], a substance which produced a powerful and prolonged pressor effect when injected into animals (1, 6). It is our purpose to report the effects of this drug upon the human circulation, since data obtained from its use in more than 800 patients indicate that methoxamine may be useful in clinical practice. The drug is effective in minimizing the hypotension associated with spinal anesthesia. In patients with low blood pressure the result of other causes, methoxamine has frequently been found of value in improving the circulation.

Pharmacologic actions. The pressor effects of methoxamine appear to be due predominantly to actions on the peripheral vascular system either at the effector cells or via the vasomotor center or both. Evidence of a direct action upon vessels is provided by the frequent observation of intense constriction along the course of a vein into which methoxamine has been injected. That the peripheral resistance is increased is indicated both by pulse pressure curves (Fig. 1) and by calculations from mean arterial blood pressure and cardiac output. Unpublished observations of Taube and Fassett show that central venous pressure is increased by the administration of methoxamine.

Cardiac rate is usually decreased, the bradycardia being particularly prominent when the drug is injected intravenously. This effect is conventionally ascribed to a reflex inhibition arising from the pressure receptors of the carotid sinus and the aortic arch. The blocking of this action by atropine (12) suggests that it is mediated over the vagus nerve.

Of note is the apparent lack of cerebral cortical stimulation. Normal volunteer subjects given the drug have noted neither change of mood nor insomnia as is so frequently observed following the administration of many pressor drugs. Therapeutic doses of methoxamine often produce a pronounced pilomotor effect which may be noted subjectively as a tingling or tightness of the skin. Spinal anesthesia does not block this pilomotor response, as it can take place in completely analgesic areas.

The drug in general resembles neosynephrine although the effect following intravenous administration appears to be more prolonged and less intense than that produced by the latter. The effect of methoxamine on the hypotension produced by spinal anesthesia is shown in Figure 1 which depicts a series of direct intra-arterial pressures recorded from the brachial artery by means of a Lilly manometer (8). A decrease in total peripheral resistance produced by spinal anesthesia is indicated by the more rapid fall of the predicrotic limb of the pulse pressure curve and the shift of the incisura toward diastolic levels. During this circulatory alteration, methoxamine was administered intravenously. This led to the production of a bradycardia (rate 60), an increase in peripheral resistance (slower fall of the predicrotic limb of pressure pulse), and a sustained increase in blood pressure. The dropped beat near the end of the record indicates an extrasystole. This effect is occasionally produced by most of the commonly used pressor amines during the early period of drug hypertension, and may be noted only by the use of continuous blood pressure or electrocardiogram recordings.

The use of methoxamine prior to spinal anesthesia. In 1946 in this clinic an attempt was made to appraise various pressor drugs ad-

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This investigation was supported (in part) by a research grant from the National Heart Institute, U. S. Public Health Service.

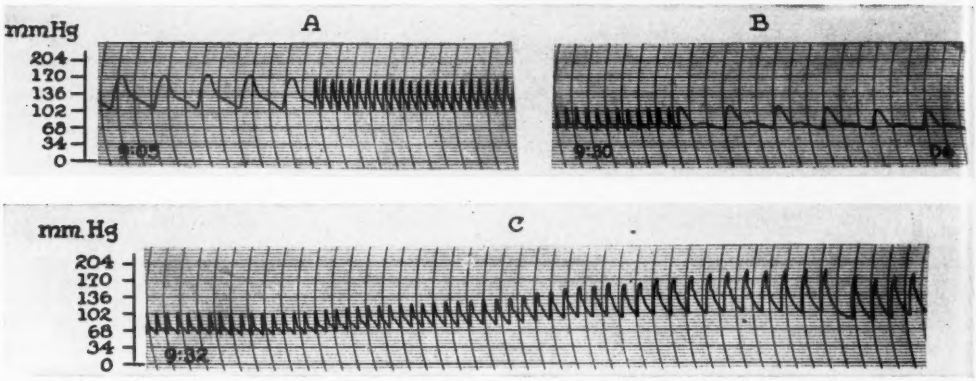

Fig. 1. Effect of methoxamine on the hypotension produced by spinal anesthesia. A, Control. Direct intra-arterial (brachial) pressure pulse contours of a hypertensive patient secured before spinal anesthesia. B, Period of hypotension 17 minutes following the administration of spinal anesthesia (pontocaine). Sensory level, sixth dorsal. C, Response to 5 milligrams of methoxamine intravenously, given 15 seconds before start of record. The space between vertical lines represents 1 second for the slower and ⅛ second for the more rapid tracings (as in A and B). See text for interpretation.

ministered intramuscularly prior to spinal anesthesia (2). Certain criteria for evaluating such agents were established in that investigation. These have been followed in the present study, so that methoxamine can now be compared to ephedrine, paredrine, a combination of pitressin-ephedrine, and methedrine, the substances surveyed in the initial report.

A series of 500 unselected patients who consequently presented most of the variables commonly encountered were given methoxamine intramuscularly in two dosage levels in order to determine its effectiveness in maintaining blood pressure during operations under spinal anesthesia. About 20 per cent of the patients received the 10 milligram dose while the remainder received 15 milligrams. The effects produced by these two doses differed so little that all of the data have been combined and treated as one.

The data are surprisingly uniform as evidenced by the histogram shown in Figure 2; extreme increases or declines in blood pressure were uncommon. The majority of patients showed no important change in blood pressure whereas in the control series the average individual showed a fall in blood pressure of 36 per cent. This indicates that methoxamine was effective in minimizing or eliminating the decrease in blood pressure commonly associated with spinal anesthesia.

As a further check on this point, the data were grouped as having or not having a fall in systolic blood pressure of 25 per cent or more, this being arbitrarily selected as a potentially dangerous decline from preanesthetic levels. In the control series, 325 patients had, and 175 patients did not have such a decrease in blood pressure; while in the methoxamine treated series, 131 had, and 366 patients did not have a decrease of 25 per cent or more. These data were analyzed statistically by means of the chi-square test for significance; it was found that $\chi^2 = 149.96$ indicating that the difference between the control and the treated patients is highly significant. Without question methoxamine was highly effective in maintaining blood pressure in this series of cases.

A. Level of spinal anesthesia. Figure 3 shows that the extent of the fall in systolic blood pressure was clearly related to the level of the spinal anesthesia. As the level of anesthesia progressed upward from sacral to cervical regions, the decline in blood pressure became progressively greater; the decrease in the control patients averaged 50 per cent when the cervical dermatomes were reached. It is interesting to note that the prophylactic administration of methoxamine raised the entire curve upward. This indicates that larger doses of the drug should be used when high levels of anesthesia are to be expected, a fact appre-

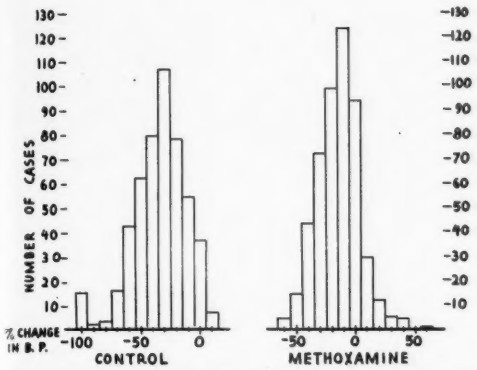

Fig. 2. Frequency distribution of maximum per cent change in blood pressure from preoperative level during operations under spinal anesthesia. The height of each bar represents the number of cases having the percentage change in blood pressure indicated along the horizontal axis.

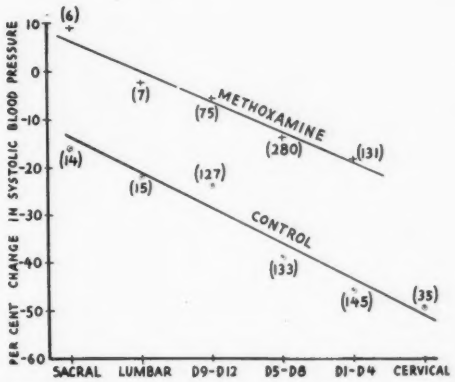

Fig. 3. The mean per cent change in blood pressure for various levels of spinal anesthesia, i.e., sacral, lumbar, dorsal 9 to 12 (*D9–12*); dorsal 8 to 5 (*D8-5*); dorsal 1 to 4 (*D1-4*); and cervical, are given for the control and for methoxamine. Note the reduction of tendency of the blood pressure to fall at each level of anesthesia following methoxamine as compared to the controls. The number of cases involved is given in parentheses.

ciated by anesthesiologists on the basis of clinical experience.

B. Type of anesthetic drug. There were no obvious relationships between the type of anesthetic agents used and changes in the blood pressure with the possible exception of "light nupercaine." The percentages of patients showing a fall in blood pressure of 25 per cent or more from preoperative level were as follows: of the 214 receiving procaine, 25.7 per cent; of the 203 receiving pontocaine, 26.6 per cent; of the 71 receiving nupercaine 1:200, 22.5 per cent; and of the 12 receiving "light nupercaine" 1:1500, 58.5 per cent. All 500 patients were given methoxamine.

C. The relationship between initial blood pressure and the fall in blood pressure. As Figure 4 shows there is a significant relationship between the level of the initial systolic blood pressure and the degree of subsequent decline. For systolic blood pressures of about 100 millimeters of mercury the average decrease was less than 5 per cent. When the initial systolic blood pressure was in the neighborhood of 150 millimeters of mercury, however, the average decrease was more than 30 per cent. This has been noted before (2).

D. Age and blood pressure fall. Despite the administration of methoxamine there were much more severe decreases in blood pressure in older people than in younger. This is shown in Figure 5 in which the average reduction in blood pressure was plotted against various age groups. The decrease tended to level off at about 50 years and to remain at a relatively constant level. The interpretation of Figure 5 is made difficult by the prevalence of certain operations in different age groups. Figure 6 shows that operations in the upper part of the abdomen were more frequent in the older age groups while those in the lower part of the abdomen tended to be more prevalent in younger patients.

DISCUSSION

The clinician has at his disposal many vasopressor drugs which are of value. The problem is one of selection. This problem of selection will be approached by analyzing certain conditions under which the administration of pressor substances may be indicated.

1. The prevention of hypotension caused by spinal anesthesia. A comparison of the ability of certain vasopressor substances to minimize circulatory inadequacy during spinal anesthesia indicated that methedrine and a combination of pitressin and ephedrine were most effective (2). On the basis of the present study conducted in a similar fashion, methoxamine might not appear at first glance in as favor-

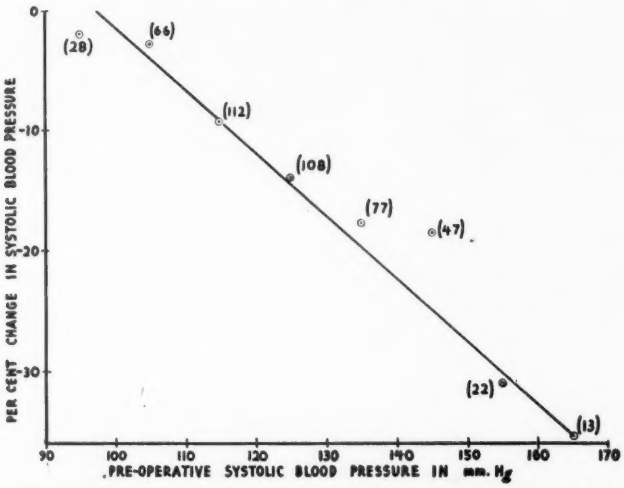

Fig. 4. The mean per cent change in blood pressure for various levels of preoperative blood pressure. The number of cases involved is given in parentheses.

able a light. Five hundred patients were studied in each group. The percentage of patients having a decrease in systolic blood pressure of 25 per cent or more was, respectively: controls, 65 per cent; paredrine, 38 per cent; ephedrine, 30 per cent; methoxamine, 26 per cent; methedrine, 20 per cent; and pitressin-ephedrine, 19 per cent. However, there are extenuating circumstances which make a further study of methoxamine indicated. Because of intestinal cramps, an increased incidence of nausea and vomiting, facial pallor and the possibility of constriction of coronary vessels pitressin is an unwise choice. Methedrine also has several disadvantages. It is a powerful central nervous system stimulant; under some circumstances this action has prevented sleep during the first 12 to 18 hours of the postoperative period. Methedrine has been observed to antagonize the sedative effect of preanesthetic medication and to render regional anesthesia less satisfactory thereby. In some patients to whom methedrine has been administered there has been an alarming and sustained rise in blood pressure, 8 to 12 hours after injection of the drug. Whether this is a cause-effect relationship is uncertain. Finally, a frequent pulse rate response to methedrine is a tachycardia which may reach 100 to 120 per minute. Methoxamine, on the other hand, has no apparent cortical stimulant action; it has not been observed to cause a delayed pressor response; and its action on the pulse rate is the production of a bradycardia. Since, as the data which are presented in this paper indicate, methoxamine has proved of real value when given intramuscularly prior to the administration of spinal anesthesia, its use under these circumstances is justified.

2. *The therapy of hypotension.* There are some circumstances under which it is proper to administer a pressor drug for the treatment of hypotension. Spinal anesthesia, assumption of the erect posture, use of vasodilator drugs and extensive sympathectomy may all be followed by hypotension which responds as a rule to vasopressor compounds. Conversely, there are other clinical states in which such drugs either accomplish little or appear to be contraindicated. Severe states of surgical shock are illustrative. In a patient with low blood pressure the value of a pressor drug will depend on two factors: the nature of the circulatory abnormality and the pharmacological property of the drug itself. Ideally, one should attempt to analyze whether hypotension is primarily the result of a diminution of total

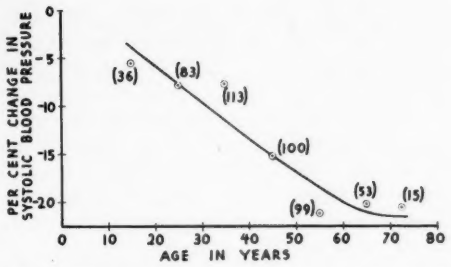

Fig. 5. The mean per cent change in blood pressure for patients of various ages. The number of cases involved is given in parentheses.

peripheral resistance, reduction of stroke volume, decrease in force of myocardial contraction, reduction in volume of circulating fluid, or alteration in viscosity of this fluid. If total peripheral resistance is decreased, an effort should be made to decide whether the vasomotor center is depressed or the peripheral vascular bed is dilated because of some local action. With the current trend toward continuous recording of intra-arterial and central venous pressure pulse contours, the estimation of blood volume, and the use of other circulatory tests, hypotension at this time is being studied more and more critically (3, 5, 9). Even further progress can be expected in this direction.

The circulatory effects of pressor drugs have also been subjected to more careful analysis. These substances can be divided into two broad categories. The first, which includes epinephrine and ephedrine, is characterized by an action on the heart resulting in increased stroke volume and heart rate. There is at the same time a diminution in total peripheral resistance indicating vasodilation somewhere (10). The second group, in which belong methoxamine, norepinephrine and neosynephrine among others, causes little or no increase of cardiac output but a distinct rise in total peripheral resistance. This apparent constrictor action appears to be exerted on both the arterial and venous systems. In the majority of instances the pulse rate is slowed following the administration of these drugs. This is a very different type of pressor activity from that which has been described for epinephrine and ephedrine.

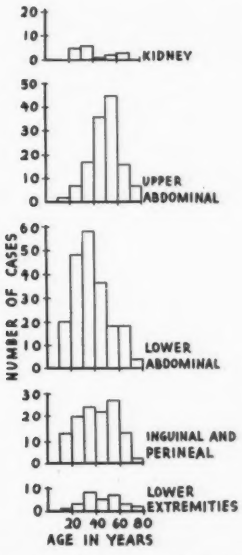

Fig. 6. Frequency distribution of patients of various ages undergoing certain types of operations.

At the present time the data available are insufficient to indicate which drug should be used for the treatment of various types of hypotension. An illustration, however, may serve to point out the type of infofmation which has proved useful. Of a series of 200 patients whose blood pressure was reduced by spinal anesthesia, it was found that in approximately 80 per cent the fundamental circulatory abnormality responsible for the lowered blood pressure was a reduction in total peripheral resistance (7). Methoxamine, norepinephrine, or neosynephrine should prove valuable in correcting this on the basis of their pharmacological activity discussed before. In the remaining patients the major alteration in the circulation was a reduction in stroke volume. A member of the first group of drugs seems indicated under these latter circumstances. As more types of hypotension are studied in this fashion, similar indications may be expected.

3. The analeptic action of certain pressor drugs. The ability of vasopressor substances to stimulate the cerebral cortex and subcortical cells varies considerably. Ephedrine and methedrine are potent cortical stimulants.

Epinephrine is not always regarded as a stimulant although many patients become anxious, tense, and irritable during its action (4). Methoxamine, neosynephrine and norepinephrine do not appear to exert any such effect. It is evident, therefore, that when circulatory stimulation is required and central nervous system depression is a factor, ephedrine or methedrine are the drugs of choice. They are useful in the treatment of narcotic poisoning and in the prevention of asphyxia neonatorum. This latter action is manifest when the drugs are given prior to delivery to mothers who have received significant amounts of analgesic or amnesic substances. When spinal anesthesia or caudal anesthesia is used by the obstetrician, it is possible for a pressor drug with the property of stimulating the central nervous system to minimize fetal depression.

Two other properties of pressor drugs should be discussed briefly. It is well known that certain sympathomimetic amines cause disorders of cardiac rhythm when administered to patients under general anesthesia. The most significant instance of this is the production of multifocal ventricular tachycardia or ventricular fibrillation during cyclopropane anesthesia by suitable doses of epinephrine, norepinephrine, cobefrin, epinine or kephrine. Methoxamine and neosynephrine appear to be the safest drugs to use when hypotension appears during cyclopropane anesthesia requiring pressor therapy. These two substances do not cause ventricular tachycardia or fibrillation, or do they accelerate the sinoauricular rate (11).

Finally there is the problem of tachyphylaxis. In the animal laboratory the repeated administration of certain vasopressor substances is characterized by a decreasing effectiveness as far as ability to raise blood pressure is concerned. If this phenomenon were applicable to man, it might be of great significance when pressor drugs are injected prior to spinal anesthesia and are subsequently required for therapy of hypotension. Or, tachyphylaxis might be obscured during the continuous intravenous drip of a solution containing a pressor drug. Pharmacologists have suggested a relationship between chemical structure and tachyphylaxis, pointing out that drugs (such as ephedrine, methedrine, and methoxamine) which have a methyl group on the second carbon atom of the side chain exhibit this property. The authors have never observed true tachyphylaxis to methoxamine. We are uncertain as to whether this response is ever of importance clinically unless relatively enormous doses are used and repeated within short periods of time.

SUMMARY

In a clinical study of more than 800 patients, methoxamine, a new pressor drug, has proved useful in preventing the decrease in blood pressure which is frequently noted after the administration of spinal anesthesia. Methoxamine has also been valuable in the treatment of hypotension of a variety of types. The prolonged action of the drug, together with its failure to produce central nervous system stimulation or to cause abnormal ventricular rhythms makes methoxamine a subsance which is worthy of further study and investigation.

Criteria for the selection of pressor drugs have been considered. The phenomenon of tachyphylaxis has been discussed.

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THE EFFECT OF EDEMA ON THE TENSILE STRENGTH OF THE INCISED WOUND

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THE possible role of edema or altered osmotic pressures as the cause of delay of wound healing in hypoproteinemia has interested several investigators. Thompson, Ravdin and Frank (10) observed marked delay in the healing of wounds of dogs rendered hypoproteinemic by diet and plasmapheresis; 72 per cent of the wounds disrupted. After 14 days of repair, few fibroblasts were present. The surfaces of the wound appeared to be bathed in a solvent that prevented agglutination of the edges, and the tissues were edematous. In a second study (11) they administered, as a corrective measure, lyophilized plasma to dogs with plasma proteins reduced sufficiently to produce edema of the tissues. After the incisions were made, 300 cubic centimeters of plasma were given daily for 6 days, and the wounds were studied on the 7th and 14th days. In spite of this replacement therapy, some edema was still observed near the edges on the 7th day but there was adequate fibroplasia and new capillary formation. After 14 days, the wounds were completely healed and there was no evidence of edema. Hence, they believed this edema, probably caused by trauma, was without effect on healing. In a third investigation from the same laboratories at the University of Pennsylvania, Rhoads, Fliegelman and Panzer altered the colloid osmotic pressure of the plasma of hypoproteinemic and edematous dogs by the administration of acacia intravenously. Serum concentrations of 2 to 3.6 grams per cent of acacia prevented edema and adequate fibroplasia occurred although the serum proteins remained low at 3.5 grains per cent. They concluded, therefore, that the deleterious effect on wound healing of low serum proteins was partially due to altered osmotic pressures and that the correction of edema was important to obtain optimal healing of tissues.

Kobak, Benditt, Wissler and Steffee (1947) studied the tensile strength of healing abdominal wounds in two groups of rats maintained on a normal diet and for 3 months on a 1.9 per cent protein diet. On the protein deficient diet, tissue edema was absent. Their results are difficult to interpret because they do not have figures to compare on the fourth and sixth days for both groups. However, on the fifth day and on the seventh day, the strength for the low protein group is significantly lower than for the control group. This suggested that on the low protein diet with weight loss, the length of the latent period of healing was prolonged.

An additional study was done to determine the possible influence of altered osmotic factors on this fifth day change. Both control and low protein rats were given 6 per cent acacia intravenously during the postoperative period while they were maintained on the respective diets. The wounds tested for strength on the fifth day in the low protein fed animals remained low while the controls were unchanged.

Since all the studies mentioned had been performed on animals with depleted proteins, it was evident that the effect of edema on wound healing in the presence of normal serum proteins should be determined.

Methods previously described for the production of edema were not ideal for studying the healing of the wound. Transient and moderately prolonged edema of the hind limbs of dogs has been produced by chemical or bacterial injury of the lumina and adventitia of the femoral and iliac veins (4, 6). With these techniques, the duration of edema could not be predicted and the presence of the large amount of damaged tissue was not desirable.

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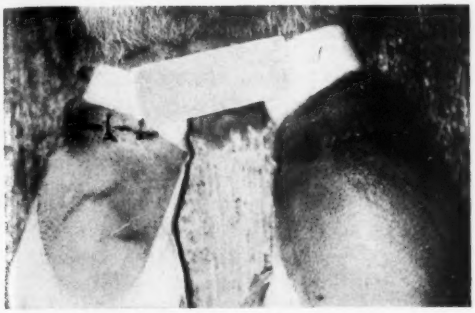


Fig. 1. Photograph of sutured wounds in control and edematous ears 1 day after operation. The tape at base of left ear supports the dressing. It is not constrictive.

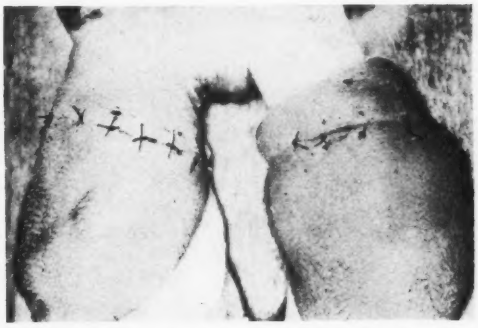


Fig. 2. Photograph of wounds 6 days after operation. Note the indentation of the scar. One suture has become untied and another has broken.

Drinker and coworkers (2, 3) produced chronic lymphedema in the hind legs of dogs by repeated intralymphatic injections of crystalline silica and quinine hydrochloride solution. This method took several months to produce a constant edema and the affected limb was more susceptible to streptococcal infections. McMaster and Hudack (7, 8) studied the role of skin lymphatics of the ears of mice in the repair of incisions and burns. This method offered intriguing possibilities but because of the paucity of tissues, special equipment would be required to study tensile strength. Finally, edema produced by constriction of the veins and lymphatics at the base of the ear of the rabbit was used.

METHOD

Giant rabbits with large ears were selected. These animals were at least 8 months old and weighed from 5 to 7 pounds. They were observed for 1 week on a Rockland chow diet before they were subjected to surgery. The ears and posterior aspects of the head and neck were closely shaved. Well fitted molds of sponge rubber were inserted inside the ears and taped in place. These flattened the pinnae of the ears allowing easier handling at operation and during postoperative treatments.

Under ether anesthesia, transverse dorsal incisions were made near the bases of both the ears approximately 2.5 centimeters long. Here the skin is freely moveable over underlying cartilage. The incisions were deepened down to but not through the fascia of the dorsal auricular muscles. Relatively little bleeding was encountered and no vessel ligatures were necessary. The large dorsal veins and arteries were avoided. The wounds were sutured with interrupted No. 00000 silk and small protective dry dressings were applied.

TABLE I.—COMPARATIVE TENSILE STRENGTHS OF INCISED WOUNDS SIX DAYS OLD ON NORMAL AND EDEMATOUS EARS OF RABBITS

Control ear	Edematous ear
289	299
398	505
284	331
286	286
200	482

Results expressed in weight (grams) necessary to pull apart the edges of a 1 cm. strip of wound. If more than one strip per wound was tested, the average result is presented.

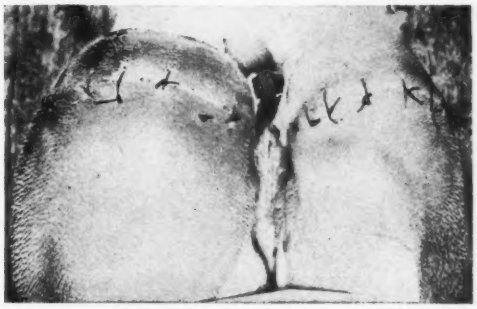


Fig. 3. Photograph of wounds in edematous and control ears 6 days after operation. Note the massive edema on the left and the stress on the sutures. One of these is untied.

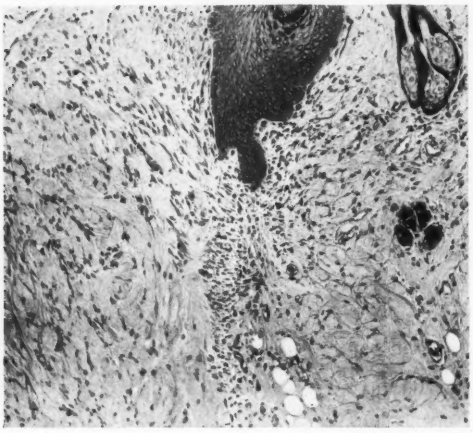
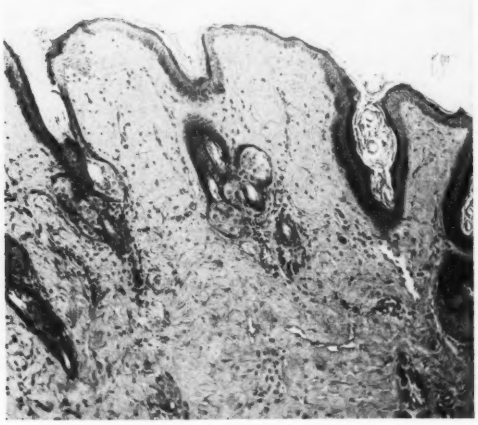


Fig. 4. Six day old wound in a normal ear. The incisional scar is relatively narrow. ×95

Six hours after operation a mildly constrictive bandage of adhesive tape was placed about the base of one ear as far away from the incision as possible while the other ear was left unconstricted to use as the control. A protective hood of muslin incorporated both ears in a single dressing and the animal was returned to its cage. The wounds and status of the edema were checked three times a day during the ensuing period of observation.

Marked edema of the entire ear could be obtained easily during the first 3 postoperative days with minimal constriction (Fig. 1). In fact, slight edema of the wound and of the skin distal to the wound occurred during this period on the control ear. After the fourth day, however, increased constriction was necessary to sustain the edema and adjustments were constantly necessary to maintain a state of marked edema and yet avoid complications. For example, if the constricting adhesive was applied too tightly on the first 2 days, a constant seepage from the wound ensued that prevented agglutination of the edges of the wound. If constriction was applied too close to the wound, the proximal skin flap tended to necrose. Lastly, the constriction could not be tight enough to interfere with arterial supply of the ear or to lower its temperature.

On the sixth postoperative day, the animals were anesthetized again, sutures were removed, and a rectangle of skin including the wound was excised from both ears. On the control ear, a cleavage plane could readily be found between the subcutaneous fat and the fascia of the dorsal auricular muscle. However, in the edematous ear, dissection was invariably more difficult due to the loss of this plane. Therefore, the underlying fascia was identified first and the dissection was made



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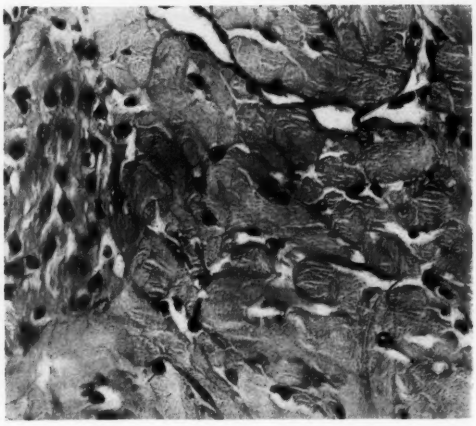


b

Fig. 5. a, Section of control ear away from wound demonstrating compact collagen and paucity of cells. ×95. b, Higher magnification of the same section as shown in a. ×370.

superficial to it. During this procedure considerable fluid escaped from the edematous ears. Before excision two 1 centimeter segments of each wound were designated by scratch marks. After removal, the segments were then excised along with adjacent skin making strips sufficiently long to test for strength. The tensile strength of the wound was measured in grams by means of a tensiometer. An adequate section of each wound was fixed for microscopic study.

RESULTS

To obtain satisfactory healing in 5 edematous ears, it was necessary to perform experiments on 12 animals. Seven animals had to be discarded because of poor healing of the edematous ear. Necrosis of the proximal skin flap occurred in 2 rabbits, chronic lymphorrhea developed in others and 2 had diarrhea.

The 5 edematous wounds that healed *per primam* showed the same characteristics grossly as the control wounds with the following exceptions. A small amount of serous fluid was occasionally noted on the dressings during the first 2 days. It usually disappeared by the third day. With marked edema on the sixth day, the tissues adjacent to the wound were elevated above the line of the incision that remained attached to underlying structures. The wound, therefore, had the appearance of a cleft (Fig. 2). The base of the cleft appeared to be covered with epithelium. A disturbing feature was the condition of the sutures. Many were untied or broken and some had pulled through the wound edges (Fig. 3).

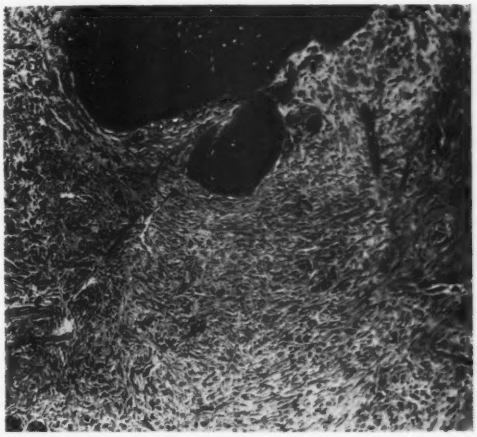
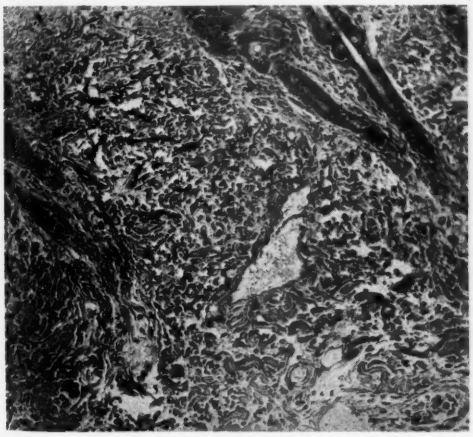


Fig. 6. Six day old wound in an edematous ear. Note the increased thickness of the scar due to increased fibroplasia at the wound site. ×95.

The tensile strengths of these wounds healing *per primam* are shown in Table I along with those for the controls. The edematous wounds were either as strong or stronger than



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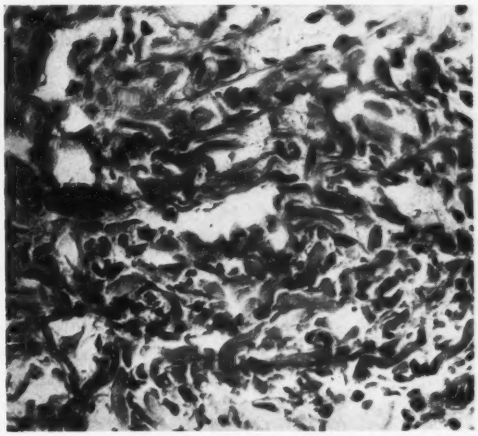

b

Fig. 7. a, Section of edematous ear away from wound showing fragmentation of collagen, increased number of cells and dilated lymphatics. ×95. b, Photomicrograph at a higher magnification of same section as shown in a. The cells present are both leucocytes and fibroblasts. ×370.

the controls. In fact, one edematous wound had more than twice the strength of its control.

Microscopically, the control incisions all healed with a thin line of immature fibrous tissue between the wound edges (Fig. 4). The fibroblasts were usually arranged parallel to the epidermis. There was no associated edema except in two wounds where it was minimal. There was infiltration of inflammatory cells, usually of the mononuclear series. New blood vessel formation was evident but lymphatics were not dilated. The tissues surrounding the wound consisted primarily of mature collagen with a paucity of cell nuclei (Fig. 5).

On the other hand, the edematous wounds microscopically revealed aberrations that explained the changes in their gross appearance and their greater strength. The epidermis was continuous. The fibrous tissue between the edges was about five times thicker than that found in the control wounds (Fig. 6). New capillary growth was evident, and all blood and lymphatic vessels were greatly dilated. Inflammatory cells were more numerous and the majority were mononuclear. When polymorphonuclear cells were observed, they appeared to be disintegrating. Throughout all sections, the collagen bundles and the cells beneath the epidermis were separated by large irregular spaces containing granular eosinophilic material (Fig. 7). Numerous young fibroblasts were infiltrating these abnormal interstices both near and far from the wound.

DISCUSSION

If the continuity of the wound was maintained through the latent period in spite of the edema, more abundant and extensive fibroplasia occurred with a resultant wound of normal or greater tensile strength. The scar was thicker and involved more of the surrounding tissues.

The edema produced in this experiment probably was due to a variety of causes. With partial venous and lymphatic obstruction, increased capillary pressure led to greater transudation of fluid into the tissues. There was faulty drainage of the extracellular water and its constituents. With the exudative process resulting from wound infliction, the protein content of the interstitial fluid increased. Although no direct measurements were made, others (2, 12) have reported that edema fluid and lymph from the same region contain approximately the same amounts of protein. The eosinophilic precipitate seen in the sections of the edematous wound and adjacent tissues suggests that the protein content of the fluid was above normal.

This type of edema caused either no change or an increase in the healing strength of the uncomplicated sutured wound. The answer why good strength resulted was found in the microscopic sections. The number of young fibroblasts between the edges of the edematous wound was invariably much greater than in the control wound. The fibrous scar was at least five times thicker. Reticulin formation took place early but polarity did not follow the lines of stress as definitely as in the control wound.

Of interest were the tissues in the edematous ears away from the wound. Here the edema caused a marked increase in the interstitial spaces and the lymphatics were dilated. There was a noticeable increase of inflammatory cells usually of the mononuclear series. Most striking was the presence of proliferating fibroblasts far from the wound edges. The presence of these proliferating cells suggests that fibroplasia seen in chronic lymphedematous postphlebitic legs occurs early in the disease. It raises the question whether an increased amount of interstitial fluid of normal or high protein content is all that is required for the proliferation and maturation of fibroblasts. In these experiments at least the process was well initiated by the sixth day after partial venous and lymphatic stasis. Certainly this experiment suggests that edema per se does not interfere with fibroplasia and wound healing if the protein needs of the cells are adequately supplied.

To the contrary, there is evidence that the presence of edema of any origin can cause mechanical changes in the continuity of the sutured wound that will adversely affect its healing. The interstitial fluid pressures may be so increased that the edges of the wound do not agglutinate. If this persists for any length of time, chronic seepage or lympho-

rhea occurs. With the failure of the wound to seal off normally by coagulated fibrin, the possibility of infections is greatly enhanced. Drinker and associates (2) have noted the susceptibility of edematous wounds to streptococcal infections and no doubt other types of bacteria can become serious pathogens.

The placement of sutures in the wound that may become markedly edematous should be done with great care because slipping of the knots can occur if they are not properly executed. Moreover, if the sutures are tied with any degree of tightness, they cut through the skin with relative ease. Particularly vulnerable must be the softer tissues of the intestinal tract when sutured, especially if they are pathologically edematous.

SUMMARY

A method of producing obstructive edema in the ears of normal rabbits is described. If the continuity of the wound was maintained, this type of edema did not lessen the acquisition of strength in the healing of sutured wounds. Fibroplasia was more marked between the edges of the wounds and at a distance from the wound in the edematous ear. Marked edema, however, can destroy the continuity of the sutured wound by destruction of the fibrin seal or the integrity of the sutures.

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EXPERIMENTAL SCOLIOSIS — THE ROLE OF THE EPIPHYSIS

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SCOLIOSIS has been attributed to a number of etiologic factors. These are variously classified but may be listed under the following general headings: (1) congenital anomalies, e.g. hemivertebrae; (2) neurologic disease with muscle imbalance, e.g. poliomyelitis; (3) rickets; (4) occupational distortions; (5) extravertebral contractures, e.g. torticollis, chest wall collapse; (6) idiopathic factors.

The patient classified under this last heading is one in whom the etiology has not been determined. This group is numerically the largest and therapeutically the most difficult to manage.

These various groups constitute an assortment of widely dissimilar factors that seem to have only one thing in common—the ability to produce scoliosis. They are said to cause the deformity by mechanical distortion of the spine. (Congenital anomalies and rickets, with their epiphyseal involvements may be more direct in their effects.) It is assumed that their asymmetric pull makes a lateral deviation of the spine. This, in turn, produces a unilateral compression of the vertebrae, so that in accordance with Wolff's law, (12) these bones acquire the altered configuration found in scoliosis.

There are, however, a number of considerations that make one question the completeness of this explanation. Why is it that the unilateral forces when applied to adults do not produce the disfiguring deformities we see in children? What is it that makes the deformity in children progress even after the deviating force is changed? How does one account for that large group of cases listed as idiopathic where no such deforming disease or occupation is recognized? Above all, why is it that the development of the deformity is essentially limited to childhood, particularly in the active growth years? A much more satisfactory explanation for these questions can be obtained if one considers the epiphysis the medium of development of the deformity.

Though the suggestion that the epiphysis is involved in the formation of spinal curvature was made many years ago, sufficient interest to prove this concept was slow in developing. In recent years there have appeared several reports on the experimental production of scoliosis by the destruction of parts of the vertebral epiphyses (2, 6). Though this experimental scoliosis is not the exact counterpart of the human deformity, in which there is no recognizable destruction of the epiphysis, the experiments are very valuable in that they establish a definite link between epiphyseal function and lateral curvature.

Our knowledge of the pathology of the epiphysis in scoliosis leaves much to be desired. Junghanns writes: "Striking changes in the intervertebral disc region cannot be recognized in early adolescent scoliosis either macroscopically or microscopically." Most of our information is based on x-ray observations, and these are necessarily indirect, since the entire intervertebral space, including the growth plate, the annulus fibrosus and the nucleus pulposus, appears as a radiolucent area between the vertebral bodies. Buchman believed that epiphyseal fragmentation as seen in Scheuermann's disease may be linked with some cases of scoliosis. On the other hand, roentgenograms of most of our developing lateral curvatures fail to show evidences of destruction, degeneration, or fragmentation. They do reveal some narrowing of the intervertebral spaces on the concave side (Fig. 1).

Even with regard to the *normal* vertebral epiphyseal plates we find our histologic information rather sketchy, though much study has been directed in the last few decades to

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the intervertebral cartilage tissue and its component parts. Microscopic studies have been made of the growing spine (9). These show, above and below the bony nucleus of the vertebral bodies, layers of cartilage that are morphologically like the growth plates in the epiphyses of the extremities. These structures are believed to be true epiphyses and the growth of the vertebral body in height is attributed to them. The intervening cartilaginous tissues, the annulus fibrosus and the nucleus pulposus and even the annular "epiphyseal" ring, are not credited with growth functions. Until growth ceases, these epiphyses are radiolucent and are, therefore, radiologically indistinguishable from the rest of the intervertebral disc.

Though we lack adequate information on the physiology of the vertebral epiphysis, much has been written about the epiphysis in the extremities. Of particular interest to us are the observations made by Delpech and by Haas. According to Delpech, "Compression produces arrest or diminution of the activity of the dia-epiphyseal cartilage, while reduced pressure causes its hyperactivity." Haas (7) demonstrated that if in a long bone the epiphyseal cap is ligated to the diaphysis, the rate of growth in the intervening epiphysis will be retarded. He also found that if he removed the ligature after a period of growth arrest, some elongation of the bone was then resumed (8).

A study of the behavior of the epiphyses in a large series of rhachitic children[1] revealed several pertinent facts. Patients with bowlegs and active rickets were treated with vitamin D and though the rickets was cured, the deformities remained. In some instances, it was noted that the deformities tended to increase for a short time after the rickets was roentgenographically healed (5). This was attributed to the manner in which bone grows at the epiphysis. Longitudinal growth takes place in a direction perpendicular to the epiphyseal plate. In a bowleg, the curve of the limb is such that the epiphyseal plates above and below the knee are not parallel to each other, but converge toward each other on the concave side. The bone elongation at these

[1]In the Harriet Lane Home, Johns Hopkins Hospital.

Fig. 1. Roentgenogram to show scoliosis in an 11 year old girl. There is narrowing of the bodies of the vertebrae and the intervertebral spaces on the concave side, without evidence of degenerative disease in the epiphyses.

epiphyses produces a tangential extension of the curve, so that the deformity appears greater. Under corrective forces, the epiphyseal cartilages become more nearly parallel and the limbs tend to straighten. The deformities in some of our patients were treated with corrective braces so that the apex of the curve was pulled toward a rigid longitudinal bar fixed on the inner aspect of the limb. Roentgenograms were taken of the knees every few weeks. It was found that the epiphyses became narrower on the convex side and broader on the concave side, thus reducing the degree of tilt of the epiphyseal plate. Under the altered plane of the epiphyseal plate, bone elongation proceeded in a direction that progressively straightened the limb. Eventually, when the extremity was straightened, the cartilage plates lost their wedged appearance and acquired the usual disc shape. The growth of the limb then continued normally (10). It appears, therefore, that when an epiphyseal plate is tilted so that one edge is compressed and the other broadened, the

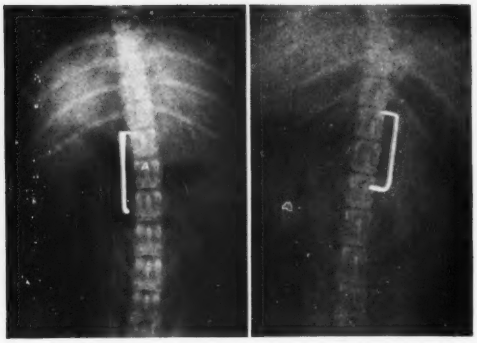

Fig. 2. Roentgenograms of a dog's spine with a staple hooked over transverse processes of lumbar vertebrae. a, left, Anteroposterior view immediately after operation, December 2, 1947. b, Similar view February 19, 1948 showing movement of the staple. There has been no development of scoliosis.

direction of bone growth is changed as the plane of the plate is changed. More exactly, it is probable that the plane of the zone of provisional calcification constitutes the directing medium.

If one applies these principles to the epiphyses of the vertebrae one can explain many of the queries that arise about the course of the scoliotic deformity. Persistent lateral tilting of the spine compresses the epiphyseal plate on the concave side and allows widening on the convex side. Bone growth is more rapid on the widened side so that the direction of vertebral elongation is at an angle to the original axis. The amount of angulation varies with the tilting of the epiphyseal plate. If the original tilting force is removed after the epiphysis has adapted itself to the new direction, growth continues in the direction of the lateral deviation. (Actually, in human scoliosis, the superincumbent spine, with its laterally displaced center of gravity, supplies a new unilateral compressing force.) The deformity is consequently progressive. Progression of the deformity is spontaneously retarded when the growth urge ceases. Adults, in whom epiphyses are lacking, tend to be immune to the formation of severe scoliosis.

One question left unanswered is, "What starts the unequal growth rate that leads to the lateral curvature in idiopathic scoliosis?" It is hardly likely that trauma is responsible since the deformity occurs far more frequently in girls than in boys. No unilateral disease or functional disturbance in the epiphyses has been established in this group. At the present time we cannot answer this question. Possibly we shall find the answer when we can explain the asymmetric growth of the extremities in hemihypertrophy.

The effectiveness of the various forms of treatment that have been used can likewise be more clearly explained if we consider the epiphysis the intermediate medium. Exercises have been recommended but in spite of the thoroughness with which these were detailed, this form of treatment has proved effective in only the mildest cases. The push-and-pull techniques, as exemplified by the Abbott treatment, have been discarded by most orthopedists as unsatisfactory. The pressures applied in these treatments are in great part absorbed by the elastic ribs before they can reach the vertebrae, so that the epiphyseal plates are hardly affected. More effective results have been obtained in the trunk-angulating procedures. In these treatments the spine is tilted in such a way that the epiphyseal pressures are changed. All forms of treatment have negligible curative value when applied to children over sixteen to eighteen. By this time the rate of growth of the epiphyses has so slackened that there is little hope for favorable epiphyseal response to corrective procedures.

Recently, fusion operations have been resorted to by an increasing number of surgeons. The American Orthopedic Association Research Committee Report (11), states: "Correction by the turnbuckle jacket and subsequent fusion has yielded better results in this series than have other types of treatment," and yet, "The results in 69 per cent of the cases at end result were rated fair or poor." In this connection, it should be recalled that when the patient stands, the deformity is usually worse than when he is recumbent. The collapse incidental to superincumbent weight is avoided. Stretching the contracted soft tissues allows a moderate straightening of the pathologic curve. If the spine is fused in the optimum position, and kept recumbent until the fusion is solid, the improved curve is re-

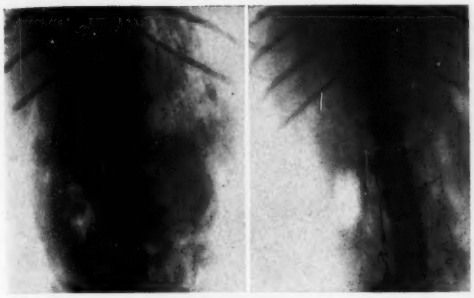

Fig. 3. X-ray views of dog's spine. a, left, Screws have been inserted into the bodies of the vertebrae on one side. The screws are bound by wire. b, When next examined by x-ray, 4 months later, the wire was found to be broken but some lateral deviation is noted. In the thoracic area there is a suggestion of a compensatory curve.

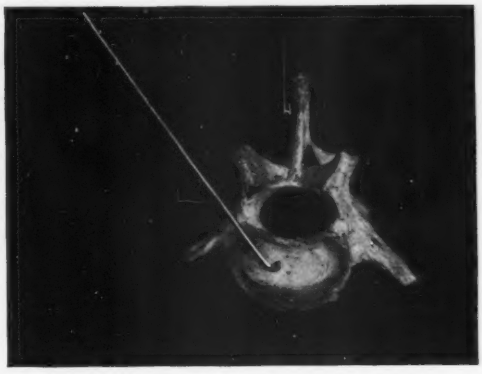

Fig. 4. Superior view of a dog's lumbar vertebra. A staple can be safely introduced into the body of the vertebra if it is driven in from the bony arch at the base of the transverse process.

tained by eliminating the collapse. Unfortunately, even this method of treatment falls under the conclusion, namely, that "practically none of the patients with scoliosis are cured, if correction of lateral deviation is a criterion" (11).

One method that has been known and used desultorily for many years needs evaluation—head and pelvic traction in recumbency. This treatment eliminates the deleterious influence of superincumbent weight with the compression of the epiphyses on the concave side. It stretches the soft tissues on the short side and eventually, by unbending the curved spine, produces some compression on the convex aspect of the epiphyseal plates. One of us has used this method since 1933, and though the series is too small to have statistical value and the results were never complete cures, there has been enough improvement in most cases to allow favorable comparison with the end results generally reported. The difficulty has been in getting the children to submit to the long bed confinement that is necessary. The redirection of the epiphyseal plates in an established curve requires more than 2 to 4 weeks of traction. A 6 month course of treatment is more in accordance with the requirements.

EXPERIMENTAL APPROACH

The belief has been often expressed that laboratory animals cannot be made to develop scoliosis because they are quadripeds and lack the disturbing forces of the erect biped. Nevertheless, if an epiphyseal dysfunction is responsible for human scoliosis, animals with similar vertebral growth structures should be susceptible to the development of lateral curvature of the spine if proper laboratory procedures are pursued. Actually, this has already been demonstrated. However, adolescent idiopathic scoliosis as seen in the human has several characteristics that must be met if the experimental deformity is to be considered simulative. These are: (1) fixed lateral deviation with varying degrees of rotation; (2) absence of evidence of disease, destruction, or fragmentation of the intervertebral space areas. Obviously, it is essential that surgical damage to the epiphyses must be avoided. Fortunately, however, selective growth control can be accomplished without direct surgical injury to the epiphyses.

Our experimental objective was to obtain unilateral compression of the bodies of the vertebrae. To eliminate the possibility of incidental procedures producing deformities, it was necessary (1) to avoid direct surgical attack on the epiphyses, (2) to keep the approach simple, with minimal damage to adjacent structures, and (3) to interfere as little as possible with the normal behavior of the animal. Several methods of obtaining compression suggested themselves, but in the interest of simplicity it was decided to bind the

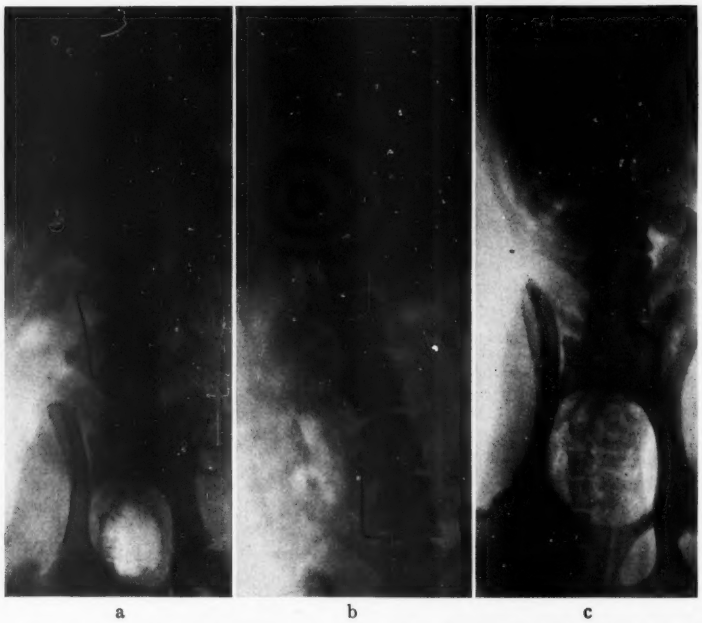

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Fig. 5. X-ray views of dog's spine. a, Nine weeks after stapling spine shows lateral deviation with rotation. Note narrowing of disc on concave side. b, Six months after stapling curvature is marked. Staple was broken and pulled out. Staple was removed immediately after this film was made. c, Seven weeks after removal of staple, deformity not only persists, but has slightly increased.

vertebral bodies unilaterally without positive compression and to allow the compression force to develop by the elongation of the growing spine against the restraining effect of the fixation apparatus.

Animals. Thirty-four dogs were used in these experiments. The exact ages of the dogs were generally not known, but most of the animals were estimated to be about 3 months old. Several 8 week old puppies were obtained. Whenever possible, we tried to get animals that could be expected to grow appreciably. We soon learned that the laboratory did not afford proper quarters in which to house the animals after operation. They were, therefore, boarded out in kennels after they had satisfactorily recuperated from the operation.

Procedure. Several different fixation apparatuses and several different surgical approaches were used before a routine technique was developed. At first a staple made of an 8 penny nail was used. This was long enough to bind three lumbar vertebrae by hooking the staple around the transverse processes of the first and third (Fig. 2). Our next method consisted of inserting screws into the sides of the vertebrae and binding the screws with a wire (Fig. 3). We finally developed a staple made of piano wire, guage 15. This is a moderately rigid wire that makes little more than a pin hole in the body of the vertebra and is not so rigid that it will break readily. Staples of various sizes were prepared, most of them 2 inches long with prongs about ⅜ inch in length.

The operative approach that was finally evolved proved to be simple and nonshocking. A longitudinal paraspinal incision was made in the lumbar area to reveal the erector spinae muscles near their lateral edge. The incision was deepened through the muscles to expose the tips of three transverse processes. With a periosteal elevator, the soft tissues were raised

medially from the posterior aspects of these processes to bring clearly into view their junction with the vertebral arch. The cortex of the uppermost vertebra was perforated at this junction, the hole being placed halfway between the upper and lower edges of the process. The lower vertebra was similarly perforated. The prongs of the staple were then introduced into the prepared holes and driven in at 60 degrees off the median plane, until they engaged the bodies of the vertebrae (Fig. 4). The soft tissues were then closed in layers and the dog was returned to its cage without external retention support.

The anatomy of the canine vertebrae differs appreciably from that of the human. In the dog, this approach does minimal damage to the soft tissues, encounters very little bleeding, and produces no recognizable shock. The angle of implantation of the staple was chosen because the wire passes through fairly solid bone and enters the vertebral body in the posterior lateral portion. In observing this direction carefully, we avoided entering the spinal canal. When the point of entry is made halfway between the superior and inferior edges of the transverse process, the clamps lodge within the body of the vertebra and do not damage the epiphyses. We thus were able to apply unilateral restraint to four vertebral epiphyses; one each in the two vertebra that were clamped and two in the intervening vertebra.

Fig. 6. Photograph of a frontal section of a dog's spine, 12 weeks after stapling of lumbar vertebrae. Note deviation of spine, narrowing of intervertebral discs on concave side and compensatory curves above.

EXPERIMENTAL RESULTS

There were 8 deaths that could be considered operative, most of them in our early experiments. Two animals were anesthetic casualties. One dog in whom an anterior approach was used died of intestinal palsy. Four deaths resulted after 6 to 11 days from infection. One animal died on the eighth day from pulmonary embolism.

Of the remaining animals 9 were treated by wiring (Fig. 3) and 17 by clamping (Fig. 7a). The wiring procedure proved to be unreliable because in every instance when, after a lapse of a number of weeks, the animal was brought back for x-ray examination, the wire was found to be broken (Fig. 3). In one dog examined 16 weeks after the operation, there was some fixed lateral deviation. In another examined after 11 weeks a slight amount of lateral angulation was found. In the others, no definite deformity was produced. Since we did not know how soon after the operation the wire broke, we can make no deductions as to the efficacy of this procedure.

In the spines that were fixed by staples, the results were far more convincing. The 2 animals with the staples hooked around the transverse processes did not show scoliosis after 3 and 6 months, respectively (Fig. 2). It is felt that the binding was too insecure to be effective. There were 15 dogs in whom the staples were imbedded in the vertebral bodies. Only 2 of these did not develop scoliosis, 1 because the clamps of the staple gave way early; the

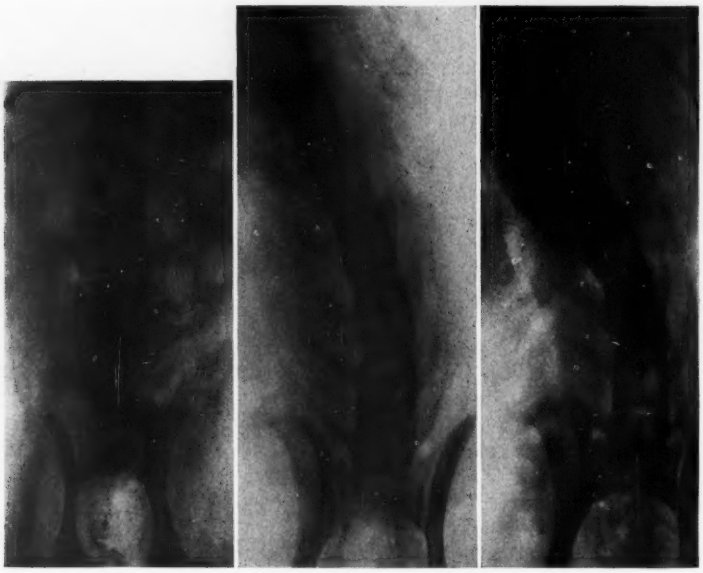

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Fig. 7. X-ray views of dog's spine. a, Four weeks after stapling. Curvature has begun. b, Four months later. The staple has just been removed. c, Six weeks later. The deformity has increased.

other because intestinal obstruction caused death 5 weeks after operation and before skeletal change was produced. All of the 13 remaining dogs developed scoliosis after a 6 weeks' lapse following operation.

Character of the deformity. In the dogs in which deformities developed, there was uniformly a fixed lateral deviation of the spine with varying degrees of rotation of the vertebrae. Since only 3 vertebrae of the entire spine were subjected to growth control, even a moderate curve assumes significance. The degree of curvature seemed to vary with the age of the animal at operation, the length of time the animal was subjected to growth restraint and the amount of growth the puppy developed in reaching maturity. The rotation varied in different animals, but this is not unexpected, since, first, the placement of the staple was not always uniform circumferentially, and second, the lateral deviations were not all of the same degree (Fig. 5). Several actually showed a compensatory curve in the thoracic region (Fig. 6). In none of the animals did the epiphyseal plates show any x-ray evidence of disease or destruction. On the concave sides of the curvatures, there was narrowing of the bony portion of the vertebral bodies and of the intervertebral cartilage space. It is interesting to note that the deformities were progressive, even after the staples were removed (Fig. 7). The similarity to adolescent scoliosis is rather striking.

It is apparent that efficient stapling of the vertebral bodies as described can be expected to produce scoliosis in young growing dogs. It is, however, necessary to assure ourselves that it is the stapling that gives the results and not one of the procedures incidental to the operation. Controls should be set up to rule out the effect of cutting the muscles and the nerves that run through them. It must also be ascertained that the burying of a foreign body along the spine is not responsible for the curvature. The necessary controls are available in the animals in whom scoliosis did not appear. In 7 of these puppies, wiring was used and in 3, staples were inserted. The

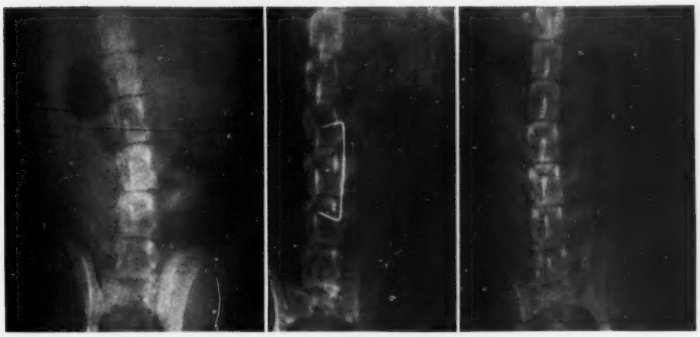

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Fig. 8. Roentgenograms of dog's spine to show correction of a fixed lateral curvature by stapling. a, One month after experimentally produced curvature has been freed from restraint. Curvature persists. b, One month after insertion of staple to correct the deformity. The lateral deviation has been straightened but the rotation persists. c, Three months after corrective stapling. Slight overcorrection has developed.

operative approaches were similar to those of the scoliotic animals. The metallic bodies were left *in situ* long enough for a satisfactory test. The postoperative care was identical in all cases. The only recognizable difference between the successful experiments and the control group is in the efficiency of the stapling. The "control" animals did not show scoliotic changes.

DISCUSSION

The scant consideration given in this presentation to the initiating factors that produce scoliosis does not indicate our belief that they are unimportant. Much has already been written about them. In this article attention is directed to the switch that when thrown by these factors turns the vertebral growth from its normal track to one of deformity. We believe that the epiphyses represent this switch, and consideration of this structure helps us explain a number of the questions about the clinical course of scoliosis. There is substantiation of this hypothesis in our ability to produce a human-like scoliosis by experimental control of the epiphyseal growth, but there is more than academic value in this concept. If growth control can curve the spine to one side, one should be able to unbend a fixed lateral curve by proper use of the same principle. In other words, the methods used in these experiments should permit the correction of scoliosis in properly selected cases. The validity of this assumption has been substantiated by us in an additional group of animals in whom a fixed lateral curvature has been cured by applying operative growth control (Fig. 8). If this process can be applied to scoliotic children it offers a hope for the cure of a condition for which no satisfactory treatment has as yet been formulated. Though the human subject presents greater technical problems than animals, the difficulty is not insurmountable. Indeed, we have already applied the same technique to 2 children who are being carefully studied for the effects of selective growth control.

SUMMARY

1. Asymmetric growth of the vertebral epiphysis is believed to be a step in the production of scoliosis.

2. Experiments that control epiphyseal growth unilaterally yield a human-like scoliosis in dogs.

3. The methods used to produce scoliosis are such they can be used for the correction of a deformity of this type.

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STREPTOMYCIN IN THE TREATMENT OF TUBERCULOSIS OF THE RECTOSIGMOID REGION AND ANUS

CLEMENT L. MARTIN, M.D., F.A.C S , and HENRY C. SWEANY, M.D., Chicago, Illinois

TUBERCULOSIS of the anal region has hitherto presented a most vexing complication in the treatment of pulmonary tuberculosis. Formerly healing was known to be spontaneous in very few cases. The principal recourse was surgical intervention, which was aided by other standard medical procedures. The reports of Chisholm, Fansler, Thomas and Kinsella (3, 4), and others have amply borne out these assertions.

Many tuberculous perianal sinuses, the so-called blind external fistulas, with or without abscesses, formerly yielding only to surgery, can now be cured without surgical intervention. The same may be said of some marginal anal tuberculous ulcers and fissures. In addition, by proctoscopic observation superficial ulcers of the rectum and sigmoid have been seen to disappear after a few weeks treatment with streptomycin. These unprecedented results, we believe, are due to the effect of streptomycin.

Less striking, but at times gratifying and even brilliant curative effects have been obtained in tuberculous patients suffering from other forms of tuberculous perianal disease, among them, true fistulas or various combinations of fistulas with the other conditions mentioned.

MATERIAL

The material in this study was obtained from cases treated on our protologic service in the last year and a half. All the patients had pulmonary tuberculosis, varying from moderate to far advanced, usually Group A or B—the majority far advanced Group B. The ages ranged from 18 to 66 years, the majority were in the fourth decade. The third, the fifth, and the sixth contained about the same number, but there were nearly twice as many in the fourth as there were in any other decade. There were 18 males and 5 females; although more men than women have perianal proctologic disease, the number of men in this series is unusually high.

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THE LESIONS

There were five types of lesions with various combinations of these five types, viz.: (1) anal or perianal ulcer; (2) anal fissure; (3) external and internal anorectal sinus—the so-called "blind" fistula; (4) true fistula with both external and internal orifices; (5) superficial ulcers of the mucosa of the rectum and sigmoid; and (6) various combinations of these.

Although well over 50 patients were treated in all, only 23 cases are deemed sufficiently complete to report at this time. Five cases will be reported in detail while all 23 are listed in Table II. All of these patients had positive sputums with streptomycin resistance studies performed on most of the bacilli isolated from the sputum. In most of the patients, the lung lesions improved, but the majority were given streptomycin for the rectal and not for the pulmonary disease.

CASE HISTORIES

CASE 1. A. M. was a 66 year old white male under treatment for pulmonary tuberculosis. In December, 1947, a perianal abscess ruptured. On admission in July, 1948, there were two sinuses, one with the external orifice in the skin of the right posterior quadrant, just distal to the anus, the other in the left anterior anal quadrant. There were no internal orifices. Streptomycin, 0.5 gram in 2 daily doses,

TABLE 1.—TYPES AND NUMBERS OF LESIONS

Perianal ulcer	1
Perianal sinus	8
Perianal abscess and sinus	5
Perianal abscess, sinus, and ulcer	1
Perianal abscess, sinus, and fissure	1
Anal fistula	5
Anal fistula with perianal abscess and sinus	1
Anal fistula with ulcer	1
Total	23

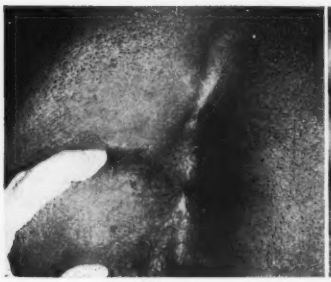

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 1. Case 2, W. N. Tuberculous perianal sinus healed by treatment with streptomycin without surgery.

Fig. 2. Case 7, E. S. Tuberculous anal fistula (before treatment) healed by treatment with streptomycin alone.

Fig. 3. Case 21, U. S. Deep extensive fistula healed by treatment with surgery and streptomycin.

was administered on July 26, 1948, and continued for 60 days. On August 24, 1948, the wounds were healing, the anterior sinus was closed, and the patient stated that there was no discharge from the posterior sinus. On September 21, 1948, both tracts were completely closed.

The result was obtained without any surgical intervention. This case well represents the other perianal sinuses (Cases 2, 3, 4, and 5) in this series with blind internal orifices. Some of these patients also had ulcers and fissures as well as sinuses. It may be concluded that most perianal sinuses, without internal orifices, will heal under treatment with streptomycin without any surgery.

CASE 7. E. S. was a 33 year old colored female, having a diagnosis of fistula in ano. She had had a perianal abscess "a few years ago" and a discharging sinus at the site intermittently since then. There were two external openings in the skin of the right posterior anal quadrant, the most anterior one of which was temporarily healed. There was a small internal opening in a crypt just to the right of the anterior midline. Streptomycin, 0.5 gram in 2 daily doses, was given intramuscularly from August 3, 1948, to October 22, 1948.

On August 31, 1948, the patient stated that there was no discharge about the anus, but a drop of pus could be expressed from the external orifice with sufficient digital pressure about the orifice. On October 19, 1948, the fistula was healed, temporarily at least. On November 30, 1948, a re-examination confirmed the statement of October 19, 1948. On December 28, 1948, the fistula remained healed, and there was no complaint.

This unusual result was duplicated in S. G. (Case 6).

In over 20 years of proctologic experience, the senior author (C. L. M.) has never seen a like result without surgical intervention. Although in these 2 cases complete fistula healed without surgery, a fistulectomy is ordinarily done. It is probably best to incise and drain all lesions having any enclosed purulent foci.

CASE 8. D. B. was a 30 year old white female with an anal ulcer. Since April, 1947, she has had periods of anal pain, not severe, but worse after defecation. Sometimes a little blood appeared on the toilet paper after cleansing. She entered the proctologic clinic on July 22, 1947, with an anal ulcer involving most of the left posterior anal quadrant and extending well out on the skin. In the past, excision of the ulcer edge and light fulguration of the base was usually done.

The patient received 0.5 gram of streptomycin twice a day from August 1, 1947, to October 1, 1947. The wound on October 15, 1947, was completely healed. No fulguration or surgery was required. The patient states that her rectal soreness and pain subsided 10 days after streptomycin treatment was started.

Healing took place without any surgical intervention. A superficial anal ulcer, therefore, responded readily to streptomycin without any surgery.

CASE 9. T. L. was a 64 year old white man with a perianal abscess, which ruptured and left a perianal sinus. On June 18, 1948, the abscess was incised and drained. A purulent drainage continued unabated, so on July 1, 1948, he was given 0.5 gram of streptomycin twice daily for 45 days. On July 13, 1949, after 2 weeks' treatment, it was observed that the sinus was healed. This result ordinarily would not have occurred before the use of this drug.

This case is fairly typical of the second group of 10 cases (Cases 9 to 18 respectively). Healing followed treatment with streptomycin and no surgery was required for repair of the

TABLE II.—STREPTOMYCIN AND DIHYDROSTREPTOMYCIN IN ANORECTAL TUBERCULOSIS

Group I. Without surgery of any kind

No.	Initials	Age	Sex	Case No.	Diagnosis (Pul.)*	Diagnosis (Proct.)	Date onset	Treatment, drug, and surgery†	Results	Time required to heal—weeks
1	A.M.	66	M	6099R	FAA	Perianal sinus	7–13–48	7–26–48 Sm. 60 days	Healed	8
2	W.N.	18	M	57131	FAB 1946	Perianal sinus	12–47	1.0 gms. Dhsm. 3–49 for 45 days	Healed	4
3	H.L.	35	M	61951R	FAA	Perianal sinus and ulcers	5–25–48	6–8–48 Sm. 60 days	Healed	6
4	J.C.	38	M	61512	FAB	Perianal sinus	12–14–48	12–3–48 Sm. 21 days	Healed	3
5	S.B.	54	M	60879	FAB	Perianal sinus	6–7–48	6–1–48 Sm. 60 days	Healed	4
6	S.G.	32	M	61864	FAB	Anal fistula with Perianal sinus	8–10–48	3–25–49 Dhsm. 45 days	Healed	12
7	E.S.	33	F	61128	FAB	Anal fistula with perianal sinus	A few years ago	8–3–48 Sm. 82 days	Healed	11
8	D.B.	32	F	59649	FAB 1947	Anal ulcer	2 months preadmission	7–31–47 Sm. 45 days	Healed	8

Group II. With only incision and drainage (or spontaneous rupture)

9	T.L.	64	M	60774	MAB	Perianal abscess, sinus and fissure	6–29–48	7–2–48 Sm. 45 days	Healed	2
10	C.S.	24	F	61416	FAC	Perianal abscess anal fistula	11–16–48	11–9–49 Sm. 45 days	(Practically) Healed	Complete in 6 mos.
11	W.P.	25	M	59550	FAB	Perianal abscess and sinus	11–9–48 1st visit	11–9–48 I. & D. 11–28–48 Sm. 12–5–48 Dhsm. Sm. 120 days	(Practically) Healed	10
12	T.M.	43	M	60570	FAC AD 3–8–48	Perianal sinus with abscess	9–47	4–7–48 Sm. 9–28–48 I. & D. 174 days	Healed	3
13	T.G.	24	M	60806	FAB	Perianal sinus	5–25–48	5–29–48 Sm. 6–15–48 I. & D. 45 days	Healed	10½
14	J.H.	48	M	60546	FAB	Perianal sinus	3–9–49	4–22–48 I. & D. Sm. 120 days	Healed	9
15	R.V.	28	M	60775	FAB	Perianal abscesses and sinuses	5–23–48	6–8–48 I. & D. 6–11–48 I. & D. 6–25–48 Sm. 60 days	Healed	2
16	D.L.	34	M	59407	FAB	Perianal abscess and sinus	4–48	5–25–48 I. & D. 6–24–48 Sm. 60 days	Healed	8
17	J.A.	34	F	61076	FAB	Perianal sinus	7–13–48 1st seen	9–17–48 I. & D. Sm. 45 days	(Practically) Healed	2
18	B.F.	23	F	61080	FAB	Perianal abscess and sinus, and rectal ulcer	7–27–48 1st visit	7–27–48 I. & D. 8–6–48 Sm. 120 days	Healed	About 8

Group III. With the customary fistulectomy

19	C.W.	20	M	60309	FAB	Perianal abscess and sinus	8–48	3–13–48 Sm. 120 days 7–10–48 I. & D. 9–7–48 Fis.	Healing well	12
20	W.Z.	41	M	61468	FAB	Fistula with Tbc. ulcer in margin	11–16–48	11–18–48 Sm. Recent fistulectomy 45 days	Healing well	4
21	U.S.	55	M	61329	FAA	Anal fistulas (extensive)	9–21–48	9–28–48 Fis. 11–5–48 Sm. 50 days	Healed	16
22	W.O.	51	M	60208	FAB	Anal fistulas (extensive)		6–18–46 Fis. 12–2–47 Sm. 6–28–48 I. & D. 60 days	Healed	1 month
23	C.T.	42	M	58281R	FAB	Anal fistula	1–47	5–18–48 Fis. 7–31–48 Sm. 2–1–49 I. & D. 120 days	Healed and recurred; healing again	8 Pract. healed

*FAA, far advanced Group A
FAB, far advanced Group B
MAB, moderately advanced Group B
FAC, far advanced Group C

†Fis., fistulectomy
Sm., streptomycin
Dhsm., dihydrostreptomycin
I. & D., incision and drainage

sinus although in all cases either an incision or a spontaneous rupture of the abscess had occurred. The healing time usually varied from 2 weeks to 3 months. In 1 case healing required 6 months.

CASE 19. C. W. was a 20 year old white male with a diagnosis of perianal abscess and sinus. When first seen, a left anterior perianal abscess was incised and drained. On March 3, 1948, the patient was given a course of streptomycin, which lasted until July 10, 1948 (120 days.) On September 8, 1948, the patient complained of pain in the perianal region. There was a residual process that was not cured by the streptomycin. The tract was thoroughly explored under anesthesia. One external orifice at 7:00 o'clock was relatively short (2 cm.) and superficial, extending toward a crypt at 7:00 o'clock. No internal orifice was found. The tract and edges were incised, and the granulations wiped out, leaving a clean base. On September 21, there appeared a perianal abscess on the opposite side in the right anterior quadrant. There was no internal orifice. The abscess was incised similarly to the primary sinus. October 19, 1949, the wound was noted as healing satisfactorily and has remained healed.

This case is a good illustration of perianal sinuses in which incision and drainage in addition to streptomycin are required for cure. It illustrates also that in certain cases abscesses will develop in spite of streptomycin, possibly because of a resistance of some of the bacilli to the streptomycin. Case 23 (C.T.) was similar.

The other 4 cases of Group III were true fistulas, some with sinuses or ulcers in which routine fistulectomies were performed. After surgery healing occurred promptly, or in less time than a group of control cases. The time of healing was about the same as that required for Group II cases.

CONTROLS

In the group of 8 controls receiving no streptomycin, there were 4 cases of perianal sinus (1 with abscess) and 4 of anal fistula. Fistulectomies or sinus incision and drainage were done in all 8 cases. Healing was complete in a month or two usually; in 1 healing occurred in 2 weeks. However, one fistula was unhealed at the end of the seventh month, and another was unhealed at the end of 8 months. The pain and discomfort experienced in this group was much more severe than in the drug-treated patients. In previous years, many cases have been too far advanced for the lesion to heal before death, a year or more after the operation.

TREATMENT

During most of this work, the patients were given 0.5 gram of streptomycin intramuscularly divided into 2 daily doses for periods of 2 weeks to 120 days, depending upon the pulmonary as well as the anorectal disease, and whether contraindications developed. Dihydrostreptomycin was given to a few of the patients begun near the end of the work, generally in 0.75 gram doses a day given in 2 daily doses intramuscularly for 45 days. Either course was repeated if necessary, when the patient was improving and showing no bad effects of the therapy. There were no untoward results, labyrinthine or otherwise.

Diagnosis was made or was confirmed, and surgical or other local treatment carried out by one of us (C. L. M. or under his direction) as proctologic patients have been treated at the institution during the last 22 years. Once a week they were re-examined. Close postoperative care was given by the resident physician.

RESULTS

Fifteen cases of perianal sinus with or without abscess healed without radical measures although surgical measures were consistently required for their cure before the use of streptomycin. In 5 of these cases no form of surgery whatever was used, in 9 a simple incision and drainage, and in 1 a fistulectomy. One anal ulcer healed completely within 8 weeks.

Two fistulas with minute internal orifices healed without surgery in 11 and 12 weeks respectively. That anorectal fistula especially could be healed without fistulectomy was a most surprising event. These 2 patients were treated 9 and 6 months ago, and thus far the wounds have remained healed.

DISCUSSION

The earnest hope of the phthisiologist for an effective antibacterial treatment of tuberculosis is being realized. Though not always a perfect curative agent in pulmonary tuberculosis, streptomycin has done more than any therapeutic agent to date. It is bacteriostatic and, in some instances, possibly bactericidal.

It suppresses tuberculous infection and permits tissue repair. It has been most useful particularly in the extrapulmonary complications as reported in this paper, including perianal lesions, either alone or in combination with surgical intervention.

A further fact suggested, but not conclusively demonstrated in this series, is that it diminishes the period of wound repair after fistulectomy. It has been our experience that it very definitely shortens the period of healing, lessens pain, and relieves other subjective symptoms, even if the cases may generally be healed by surgery alone.

It is understood that fistula in ano and perianal sinuses are extremely variable entities; either may be very superficial and the infected tract short, or they may be deep, branching, and extensive, especially in the case of a true tuberculous fistula. Therapeutic results must be evaluated with this in mind. In spite of the fact that in 2 cases of fistula with small "pin point" internal orifices healing occurred without fistulectomy after streptomycin treatment, a fistulectomy is ordinarily necessary in cases with internal orifices.

In other cases of anal or anorectal fistula which were operated upon during the last year and not included in the series, streptomycin was given before or after operation, usually both. Results were similar to those reported.

The perianal or perianorectal abscess which precedes the sinus is probably the result of an infection originating in the anal crypts or ducts leading from them or in tissue immediately adjacent to them. It is located in or about the stratified pavement and transitional epithelium of the upper (cephalic) part of the anal canal and extends by lymphatic channels and by direct continuity in the tissues. Cryptitis and anal duct infection, therefore, are generally regarded as the usual cause of most deep anal and perianal lesions.

Although all the patients had positive sputums for tubercle bacilli, there may be a question raised as to the tuberculous nature of the lesions. In previous studies criteria of diagnosis were discussed and the tuberculous nature was proved by serial sections in 72 per cent of the cases. It is probable that the true percentage is still higher.

An occurrence worthy of reporting is the development of perianal abscess during the regular treatment of pulmonary lesions with streptomycin. Four such cases have been observed—2 in this series (Cases 19 and 23).

Although in the original study their inclusion was not contemplated, it was noted that healing was greatly aided in cases of perianal ulcer (Case 1) and in tuberculous enterocolitis with ulcers visible proctoscopically. Seven of the latter were followed by proctoscopic study and healed during the course of treatment.

SUMMARY

A report has been presented to show the effect of streptomycin treatment alone, or with the aid of surgery, on perianal tuberculosis. Tuberculous perianal sinuses, that is, sinuses with external, but no internal, orifices, have been found to heal without surgery as a result of the use of streptomycin.

Perianal abscesses, however, still require the intervention of incision and drainage.

Although 2 small fistulas in this series healed without surgical intervention, complete or true fistula in ano, that is, those having internal and external orifices, generally require surgery before complete healing takes place.

Superficial lesions such as anal ulcers, fissures, and ulcers in the mucosa of the rectum and sigmoid normally heal promptly and completely following streptomycin treatment.

A most important observation was that the patients treated with streptomycin have far less severe subjective symptoms, both before and after surgery. Almost always distress and pain were relieved within a few days after streptomycin treatment was begun.

In a certain small percentage of cases, abscesses formed during streptomycin treatment perhaps due to the development of resistance in some of the tubercle bacilli in the local lesion.

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BLOOD VOLUME DETERMINATIONS IN SURGERY

An Analysis of 100 Cases

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ROUTINE determinations of the percentage of hemoglobin and erythrocytes, plasma proteins, hematocrit, and plasma sodium chloride in any specimen of blood usually do not reflect accurately the circulating hemoglobin and erythrocyte masses, circulating plasma volume and circulating plasma proteins. Reduction of blood volume, circulating hemoglobin mass and circulating plasma proteins predisposes to development of shock either during operation or in the early postoperative period (1, 4). Practical methods of determining plasma volume with Evans' blue (T-1824) were described by Gregersen, by Gibson and Evans (6), and by Gibson and Evelyn(7). These methods, used experimentally by various investigators, were recently utilized by us as a portion of a simple system of evaluation of surgical risk suitable for the average hospital (2). The evaluation is based on calculating from laboratory tests plasma volume, total blood volume, circulating hemoglobin mass, and circulating plasma proteins. These are compared with estimated normal values and the corresponding deficits determined.

The purpose of this communication is to present 100 consecutive cases of major surgery in which evaluation of the preoperative status was made and in which restoration of the deficient elements before operation and replacement of blood loss at operation were accomplished. The extent of the deficits of the various elements will be shown and their significance will be discussed with particular reference to estimation of surgical risk.

DISTRIBUTION OF CASES

Blood volume and other studies were performed in all cases presented herein. Such studies were limited to surgical cases of major import and the 100 consecutive cases are listed in Tables I and II.

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LABORATORY DATA

The following laboratory determinations were made in each case: erythrocyte count, hemoglobin grams per 100 milliliters, hematocrit, specific gravity of the plasma and whole blood, plasma proteins grams per 100 milliliters and plasma volume by the Evans' blue method. In addition each patient's blood was tested for Rh factor and group and was crossmatched with as many pints of blood, from the blood bank, as were likely to be required before and during operation. All values obtained from these tests were sent to the proper nurses' station in the hospital where they were recorded on a surgical evaluation chart. We strongly recommend that one person be responsible for the calculations which are necessary after the above data have been recorded. While our assistant surgical resident bears such responsibility, the average hospital without residents or even without internes may delegate the duty to the pathologist or head laboratory technician. This delegation of responsibility is of the utmost importance as the proper evaluation of surgical risk depends upon the accuracy of the calculations from the original laboratory data.

At the top of the surgical evaluation chart are recorded the patient's name, age, and hospital number. On the line beneath, the name of the doctor and the diagnosis are provided for. All headings for the other data should be placed in the left vertical column and there should be 7 other columns across the sheet representing the 7 days of the week, similar to a temperature chart. The recommended headings are shown in Chart 1.

The expected values are calculated on the basis of normal weight by the formulas in parentheses. When the patient is extremely

TABLE I.—DISEASES IN SERIES OF 100 CASES

Disease	No. cases
Hyperthyroidism	4
Substernal goiter	1
Carcinoma of esophagus	4
Diaphragmatic hernia (esophageal hiatus)	1
Carcinoma of stomach	9
Gastric ulcer (nonmalignant)	6
Gastrojejunal ulcer	3
Diverticulum of cardia with ulceration	2
Gastrojejunocolic fistula	3
Duodenal ulcer	24
Cholelithiasis and cholecystitis	14
Cholelithiasis and cholecystitis with perforation and abscess	1
Carcinoma of pancreas	5
Acute pancreatitis	3
Obstruction of small intestine	6
Regional ileitis	1
Carcinoma of cecum	1
Carcinoma of transverse colon	1
Carcinoma of sigmoid	3
Carcinoma of rectum	4
Diverticulitis of sigmoid with perforation	1
Diverticulitis of sigmoid with perforation and vesico-sigmoid fistula	1
Adenomyosis uteri	1
Carcinoma of uterine fundus	1
Carcinoma of ovary	1
Massive ventral hernia	1
Carcinoma of breast	3
Retroperitoneal lymphosarcoma	1
Hemofibrothorax	1
Massive ulceration of leg	1
Empyema thoracis	1

CHART I.—SURGICAL EVALUATION CHART DATA

		Normal	Present
Weight in kilograms (lbs.÷2.2)			
Height in centimeters (in.×2.54)			
Hematocrit			
Hemoglobin, grams per 100 milliliters (16.3)*			
Plasma proteins, grams per 100 milliliters (7.0)			
Whole blood specific gravity (1.055)			
Plasma specific gravity (1.025)			
Total blood volume	expected (kgm.×85)		
	determined		
	deficit		
Plasma volume	expected (kgm.×45)		
	determined		
	deficit		
Cell volume	expected (kgm.×40)		
	determined		
	deficit		
Circulating hemoglobin	expected $\frac{(TV \times 16.3)^*}{100}$		
	determined		
	deficit		
Circulating proteins	expected $\frac{(PV \times 7.0)}{100}$		
	determined		
	deficit		
Total body proteins	deficit (circ. prot. deficit×30)		

*This value is our standard for 100 per cent hemoglobin. Any other standard may be substituted but must be used in all formulas.

TABLE II.—OPERATIONS IN SERIES OF 100 CASES

Operation	No. cases
Subtotal thyroidectomy	5
Transthoracic resection of carcinoma of esophagus	3
Transthoracic resection of cardia	1
Total gastrectomy, transthoracic	1
Repair of esophageal hiatus hernia, transthoracic	1
Subtotal gastric resection	32
Subtotal gastric resection with excision of marginal ulcer	3
Gastrostomy	1
Gastrojejunostomy	4
Cholecystectomy	14
Cholecystojejunostomy	4
Lysis of obstructive adhesions and bands	6
Laparotomy, with or without drainage	9
Right hemicolectomy with ileotransverse colostomy (one stage)	1
Transverse colostomy	3
Resection of transverse colon with primary anastomosis	3
Ileotransverse colostomy	2
Resection of sigmoid with primary anastomosis	1
Obstructive resection of sigmoid	2
Abdominoperineal resection	4
Repair of vesicosigmoid fistula	1
Ventral hernioplasty	1
Radical mastectomy	3
Panhysterectomy	3
Pulmonary decortication	1
Thoracotomy and drainage	1
Excision of ulcer of leg and tendon with skin grafting	1

thin or obese, standard weight, height, and age tables should be used. Once the plasma volume has been determined, all other determined volumes may be obtained by using the formula: PV/BV = Hpl/100, where PV represents plasma volume, BV total blood volume, and Hpl the percentage of plasma obtained by subtracting the hematocrit from 100. The total amount of circulating hemoglobin and proteins may be computed as follows:

$$\text{Total Hgb.} = \frac{BV \times \text{Hgb. (gm.\%)}}{100}$$

$$\text{Total circulating protein} = \frac{PV \times \text{Pl.prot. (gm.\%)}}{100}$$

The determined values, as calculated above, are entered on the chart below the estimated values and the deficits or excesses obtained by subtraction. The total body protein deficit is the total circulating protein deficit multiplied by 30. A more detailed description of our methods has been published (2).

EVALUATION OF DEFICITS

After the various deficits have been calculated, according to the methods described.

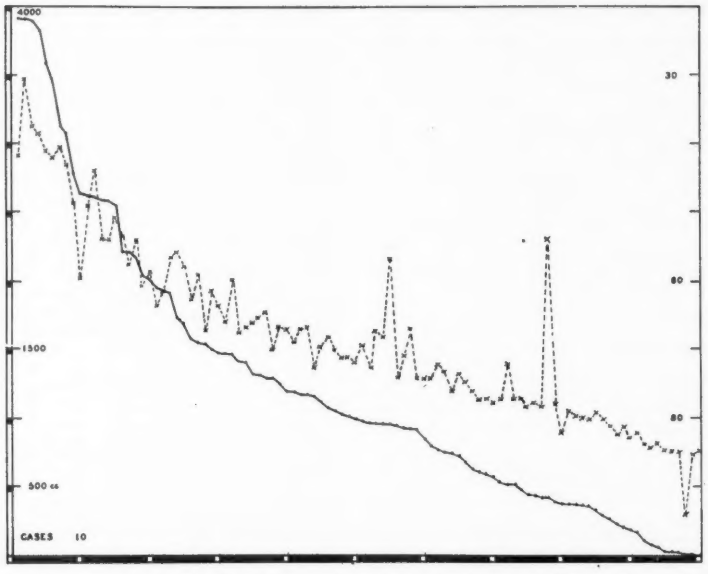

Fig. 1. Showing parallelism between blood volume deficits and blood volume per kilogram. Such parallelism exists only between deficits and per kilogram values and *not* with ordinary hemoglobin, hematocrit, and plasma protein values. •—•—•—•—•, blood volume deficit; x————x, blood volume per kilogram.

what do they mean? How much blood volume deficit is significant?

In estimation of blood volume, or more correctly plasma volume, there will be certain errors inherent in the method itself which we may call the experimental error. The other source of error in the final result is due to physiological error. Evans' blue dye, according to Peters, can be detected within 5 minutes in high concentration in thoracic duct lymph. In other words, there is leakage of dye into the extracellular spaces and, as a result, there is more dilution of the dye than would be expected if no leakage took place. The plasma volume values calculated from this test with Evans' blue (T–1824) are greater than those obtained by the carbon monoxide method, since the carbon monoxide attaches itself to the red blood cells.

We have frequently been questioned about the accuracy of plasma volume determinations with Evans' blue (T–1824) by physicians who rely in daily practice on erythrocyte counts, leucocyte counts, mean corpuscular volume, and various other clinical tests. These tests seem to be taken for granted. They are, however, subject to wide variations, the limit of significance in red cell counts being ± 20 per cent, for example. We strongly recommend the reading of recent critical surveys of common laboratory tests by Belk and Sunderman and by Ham.

Our experience has shown that with redetermination of plasma volume in the same individual the error is less than the 5 per cent reported by Gibson and Evans (6).

We believe that, as compared with routine laboratory tests, determination of blood volume with T–1824 and calculation of deficits as recommended are reasonably accurate clinically and the most reliable tests available.

Inasmuch as Gregersen has reported 96 per cent of normal values for plasma with the carbon monoxide method, and 103 per cent with the T–1824 method, there is about a 5 per cent experimental error.

Let us concede, therefore, that there must be a greater error than 5 per cent due to the

added physiological variations and assign an error up to 10 per cent to allow for both. Then, deficits over 500 milliliters in adults are significant. This means that in those patients with a total blood volume of 76.5 milliliters per kilogram, a plasma volume of 40.5 milliliters per kilogram, and a cell volume of 36 milliliters per kilogram, replacement of the deficit is mandatory. Any deficit of 500 milliliters or more in the total blood volume must be made up before a patient can be considered a good operative risk. With this as the basis, there was a significant deficit of blood volume in 75 per cent of our patients. In our series of 100, deficits ranged from 4,000 milliliters to zero, and the cases are numbered consecutively from greatest deficit to lowest.

It will be readily understood, therefore, that in estimating plasma volume and total blood volume in the method that we use, larger values are obtained for blood volume than with carbon monoxide and, therefore, smaller deficits. This may account in part for the fact that we have had no trouble with overloading of the vascular system even though slightly more than the deficient elements often were replaced.

Fear has been expressed regarding blood replacement in the presence of cardiac disease. Quantitative replacement is, we believe, more important in such cases than in those patients without heart disease and may make the difference between death and a successful outcome. Saline solutions, however, should not be given.

It must be remembered that a small deficit in a small individual is just as serious as a large deficit in a large individual. Consider, for example how much 250 milliliters of blood represents of a baby's total blood volume.

The seriousness of the deficit, therefore, is directly proportional to its value in percentage of total volume. This also may be correlated with the blood volume per kilogram, a reflection of weight, and may be seen in Figure 1.

It must be stressed that large deficits of protein cannot be made up within a few days by whole blood, plasma, or protein administration. Preoperative blood volume replacement cannot be expected to correct severe protein deficit overnight. It will, however, correct blood volume deficits. We have been able to restore both blood volume and body protein stores by diet alone within a few weeks as evidenced by positive nitrogen balance, weight gain, and determined blood volume increase.

All deficits should be made up whether they be large or small but a smaller deficit should not be ignored in relation to a larger one nor should it be minimized without first taking into account the weight of the individual.

The quantitative replacement of blood volume deficits preoperatively and blood loss during operation has, in our hospital, almost eliminated postoperative shock, has widened the scope of surgery, and has lowered mortality and morbidity. Postoperative convalescence has been rapid in patients thus treated as compared with the slow recovery of many patients not receiving the benefit of replacement. Without restitution, red cell volume recovers slowly. Lyon and associates have shown that, with blood losses of 500 milliliters or more, restoration by hematopoiesis is slow and frequently minimal during at least 10 days after the loss and when there are larger deficits, restoration may be incomplete for as long as 2 months after operation. Their findings give further evidence of the importance of adequate preoperative replacement.

WHAT IS BLOOD VOLUME DEFICIT?

A blood volume deficit must be, as the word states, a deficit of circulating blood and, therefore, of its various components. It consists of a deficit of one or both of cells and plasma. In other words, any two or more identical total blood volume deficits may have entirely different percentages of the two components. In fact, of the first 75 cases only 12 patients had proportionate excess plasma deficits.

The following case is not in the series but is so striking that it is used as an example of plasma volume deficit.

G.M., O.H. No. 71445, a 64 year white male, was seen in consultation at another hospital. He had had a cholecystectomy and exploration of the common duct with removal of stones. He was first seen by us on the 28th postoperative day at which time he was suffering from dehydration, fever, and lassitude. Blood volume estimation showed the following:

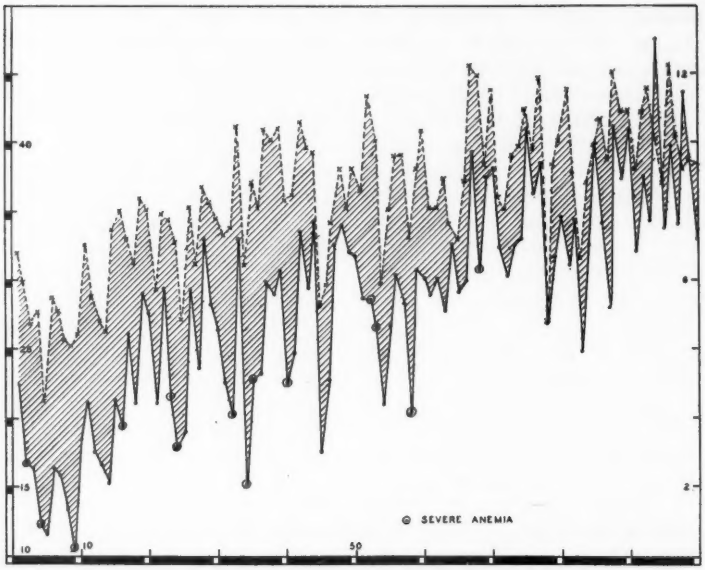

Fig. 2. Cell volume per kilogram and circulating hemoglobin per kilogram closely parallel each other except when there is severe anemia or hemoglobin deficit. The circles indicate 14 cases of such excessive hemoglobin deficit. •————•, cell volume per kilogram; x————x, circulating hemoglobin per kilogram.

Total blood volume deficit	848 ml.
Plasma volume deficit	1,125 ml.
Circulating protein deficit	99 gm.
Cell volume difference	+280 ml.
Hemoglobin deficit	53 gm.

He was given 1,500 milliliters of plasma on the 30th postoperative day followed by immediate improvement and ambulation.

Since we have assigned 500 milliliters as the point of significance for total blood volume deficit it follows that a plasma deficit of 275 milliliters and a cell deficit of 225 milliliters are significant. It is interesting to note that 60 per cent of the patients had significant cell deficits.

OTHER DEFICITS

Hemoglobin deficit. This and not the cell volume deficit is the more important because the oxygen carrying capacity of the blood is directly proportional to the amount of circulating hemoglobin. Replacement should be made on the basis of hemoglobin deficit and not on cell deficit. In Figure 2 it will be noted that the cell volume per kilogram sometimes does not disclose severe hemoglobin loss although there is definite parallelism. The discrepancies are due to severe anemia or hemoglobin deficit. For this reason the amount of whole blood or the amount of cells given should be calculated on the basis of hemoglobin content which is, after all, oxygen carrying capacity. The following cases illustrate relative hemoglobin and red cell mass deficits:

R.M., St.B.Hosp. No. 76437, a 40 year white male, had had: increasing epigastric pain for 6 months; one episode of hematemesis and tarry stools; tenderness in the epigastrium; and roentgen evidence of much duodenal deformity. The diagnosis was duodenal ulcer. Preoperative surgical evaluation:

Total blood volume deficit	3,820 ml.
Plasma volume deficit	1,500 ml.
Circulating protein deficit	118 gm.
Cell volume deficit	2,330 ml.
Hemoglobin deficit	751 gm.

This patient underwent a subtotal gastric resection. He received 2,500 milliliters of whole blood preoperatively; 1,000 milliliters of whole blood while on the operating table, and made an excellent recovery, being discharged from the hospital on the 9th postoperative day.

O.J., St.B.Hosp. No. 69982, a 60 year white male, had had generalized weakness, pain in epigastrium,

and weight loss of 10 pounds in the previous 6 months; coronary heart disease of 7 years' duration; tenderness in the epigastrium with suggestion of a mass; roentgen evidence of gastric neoplasm. Electrocardiographs disclosed coronary heart disease. The diagnosis was carcinoma of the stomach and coronary heart disease. Preoperative surgical evaluation:

Total blood volume deficit	3,899 ml.
Plasma volume deficit	1,970 ml.
Circulating protein deficit	140 gm.
Cell volume deficit	1,929 ml.
Hemoglobin deficit	749 gm.

This patient had a laparotomy which revealed carcinoma of the stomach with metastases. An extensive dissection with almost complete resection of the stomach was done. He received 3,000 milliliters of whole blood preoperatively, 500 milliliters while on the operating table to cover estimated loss, and 1,000 milliliters postoperatively. He developed a wound infection which prolonged his hospital stay to 26 days.

The most frequent finding in our patients was a relative hemoglobin and cell deficit. This is plainly shown in Figure 3 in which the plasma deficits are charted in terms of percentage of total blood volume deficit. If any blood volume deficit be made up of the normal percentages, then 55 per cent would be plasma and 45 per cent cell deficit. Of Cases 1 to 80, only 14 patients had relative excess plasma deficit. The vast majority showed cell deficits of import.

It is evident, therefore, that in our series, at least, and probably in other similar series the greatest need is for erythrocyte replacement. Most deficits, however, are composed of both elements. When the hemoglobin or cell deficit is disproportionately severe, then administration of a suspension of erythrocytes is better than whole blood, but such suspensions are not readily available except in a few centers.

CIRCULATING PROTEIN AND BODY PROTEIN DEFICIT

The circulating protein deficit is an index of the body protein deficit, the latter being 30 times the former. It further indicates disturbance in protein metabolism such as inadequate intake, poor absorption, and faulty utilization. The ill effects of reduced circulating protein have been discussed fully by many writers and the calculation of such deficits by the methods outlined gives warning that edema

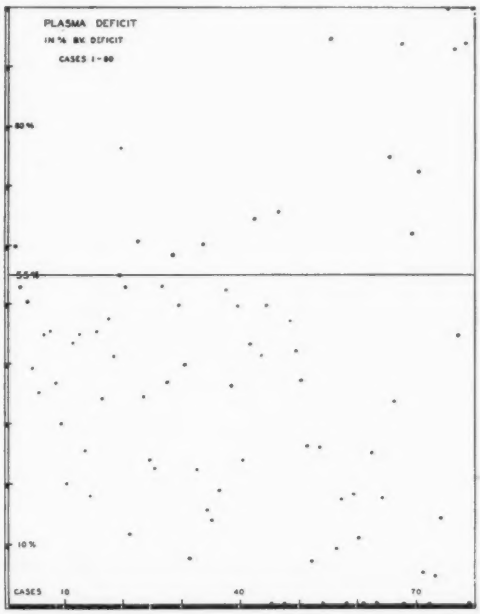

Fig. 3. Since 55 per cent of blood is plasma, then by plotting plasma deficits in terms of percentage of blood volume deficit, the distribution around the normal 55 per cent line is shown. In this series relative hemoglobin or cell deficits predominate.

of anastomotic stomas, delayed wound healing, and dehiscence, for example, may occur.

The following cases show relative deficiencies of total circulating and body protein:

R.P., St.B.Hosp. No. 72030, a 50 year white female, had a history of 20 years of an ulcer diet with recurring episodes of epigastric pain; 2 severe gastric hemorrhages in the past 3 months; tenderness in the epigastrium; and roentgen evidence of gastric ulcer. Preoperative surgical evaluation:

Total blood volume deficit	3,920 ml.
Plasma volume deficit	2,340 ml.
Circulating protein deficit	168 gm.
Total body protein deficit	5,040 gm.
Cell volume deficit	1,580 ml.
Hemoglobin deficit	632 gm.

This patient underwent a two-thirds subtotal gastric resection. She received 2,000 milliliters of whole blood and 1,000 milliliters of plasma preoperatively and 1,500 milliliters of whole blood while on the operating table. Estimated loss during operation was 500 milliliters. She had a satisfactory postoperative course and was discharged 16 days after operation.

A.B., St.B.Hosp. No. 65832, a 54 year white male, had epigastric pain with eructation and vomiting for

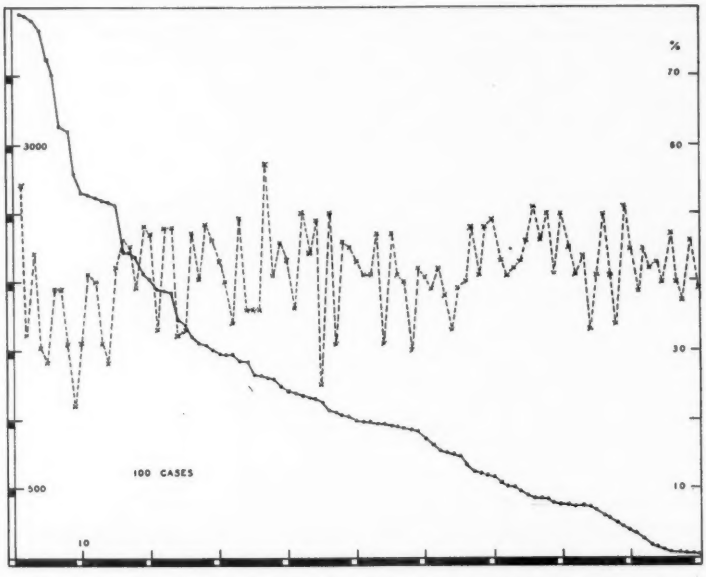

Fig. 4. Showing the lack of parallelism between blood volume deficit and hematocrit. Deficits are plotted in descending order from greatest to smallest. Hematocrit gives the percentage of packed cells in any sample of blood but cannot indicate total amount of circulating blood. •—•—•—•, blood volume deficit; x———x, hematocrit.

4 weeks; tenderness in the epigastrium; roentgen evidence of diverticulum of the cardia at the esophagus and a larger ulcerating lesion on the lesser curvature. Preoperative surgical evaluation:

Total blood volume deficit	1,939 ml.
Plasma volume deficit	1,176 ml.
Circulating protein deficit	74.2 gm.
Total body protein deficit	2,226 gm.
Cell volume deficit	763 ml.
Hemoglobin deficit	471 gm.

The patient had a transthoracic total gastric resection, with esophagojejunostomy and splenectomy. He received 1,000 milliliters of whole blood before operation and 1,000 milliliters of whole blood plus 750 milliliters of plasma at operation. Another 500 milliliters of whole blood were given postoperatively.

The following cases are instances in which more than one blood volume determination was made. They demonstrate the accuracy of the procedure.

W.B., St.B.Hosp. No. 62606, a 58 year white male, had a diagnosis of carcinoma of the pancreas. Blood volume estimations were done 2 weeks apart with no administration of blood or plasma and no surgery between the two determinations.

E.M., St.B.Hosp. No. 72398, a 49 year white female, had a diagnosis of incomplete small bowel obstruction due to postoperative adhesions. Blood volume determinations were done 3 weeks apart and the patient received 1,000 milliliters of whole blood and 500 milliliters of plasma between estimations.

BLOOD VOLUME DETERMINATIONS, CASE W. B.

	Expected values	1st determination	2nd determination
Total blood volume	6,205 ml.	6,083 ml.	6,167 ml.
Plasma volume	3,285 ml.	3,346 ml.	3,187 ml.
Cell volume	2,920 ml.	2,737 ml.	2,980 ml.
Circulating plasma protein	229.9 gm.	229.5 gm.	229.9 gm.
Circulating hemoglobin	930.8 gm.	803 gm.	814 gm.

BLOOD VOLUME DETERMINATIONS, CASE E. M.

	Expected values	1st determination	2nd determination
Total blood volume	5,030 ml.	4,545 ml.	5,750 ml.
Plasma volume	2,650 ml.	2,590 ml.	3,220 ml.
Cell volume	2,370 ml.	1,955 ml.	2,530 ml.
Circulating plasma protein	186 gm.	164 gm.	217 gm.
Circulating hemoglobin	818 gm.	590 gm.	820 gm.

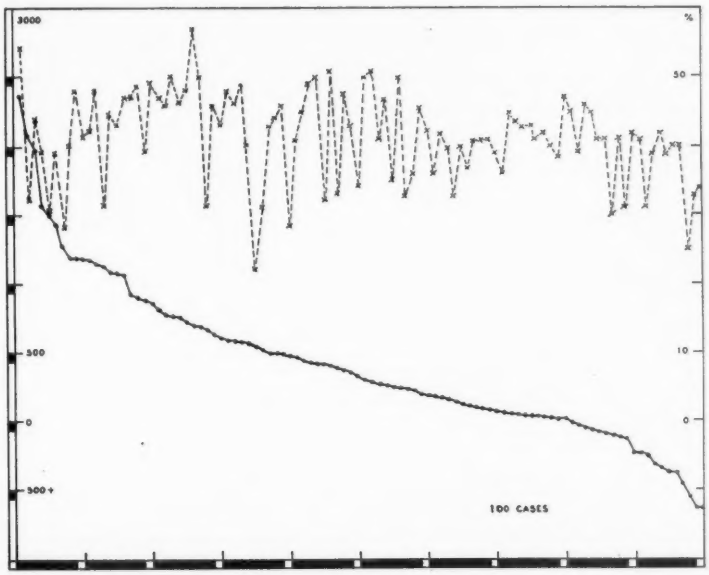

Fig. 5. The hematocrit values do not parallel the plasma deficit values, the lack of correlation being similar to that in Figure 4, when plotted against blood volume deficit. •—•—•—•—•, plasma deficit; x————x, hematocrit.

ORDINARY LABORATORY TESTS

We previously called attention to what we thought was a lack of correlation between the deficit values and the hematocrit, hemoglobin grams per 100 milliliters and plasma protein grams per 100 milliliters. The present series of cases offers conclusive proof that such correlation does not exist (Figs. 4, 5, 6). The most striking lack of correlation is evident in Figure 7 in which the hemoglobin grams per milliliter values are so far from mirroring the circulating hemoglobin deficits as to be disastrously misleading if relied upon. It will be seen in Figures 4, 5, 6 that there is no reliable correlation between blood volume deficit and hematocrit or plasma volume deficit and plasma protein grams per milliliter concentration.

Parallelism does exist, however, between blood volume deficit and blood volume per kilogram (Fig. 1) and between figures for plasma, cells, hemoglobin, and plasma protein.

EVALUATION OF OPERATIVE RISK

In our opinion the most important means of estimating operative risk, after ruling out disqualifying cardiac and renal defects, is the determination of the data presented herein. From such data deficits of water, hemoglobin, circulating protein, and body protein may be discovered quickly and simply. We recommend also that the plasma sodium chloride concentration per 100 milliliters be determined so that restitution may be made, if necessary, or that an excess may be revealed. We realize that this value is not, in all probability, a reliable one and believe that replacement on the basis of total circulating mass should be more accurate. Our results with this type of replacement will be reported later. In our hands, the recognition of these deficits and their preoperative correction have led to lessened morbidity, increased scope of surgery, and lowered mortality, particularly in patients previously considered poor risks.

There are still many surgeons who believe that the blood volume and nutritional status of a patient are reflected adequately in the erythrocyte count, hemoglobin concentration per milliliter, hematocrit, and plasma protein concentration per milliliter. If the erythro-

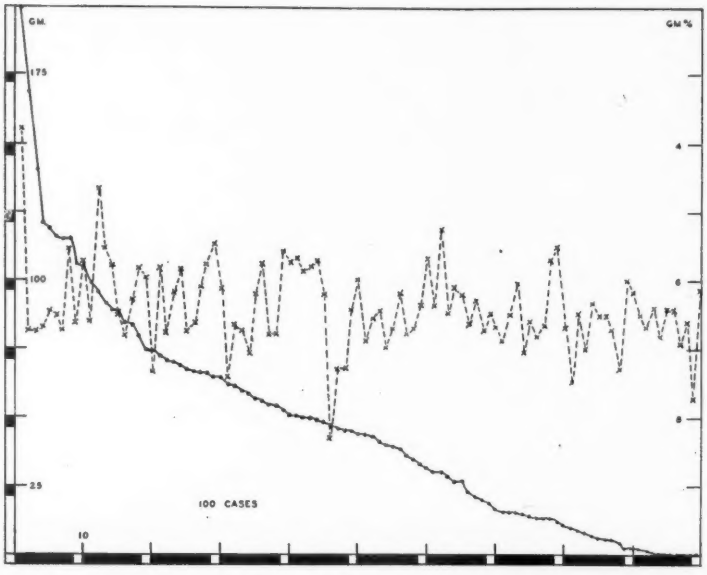

Fig. 6. There is no parallelism between the plasma protein values, in terms of grams of protein per 100 milliliters, and the circulating protein deficits. The plasma protein values are plotted so that the lower values are opposite the greater deficits, and if they were good indicators of the circulating proteins, then their curve should run from the upper right downward to the lower left of the chart. •—•—•—•—•, circulating protein deficit; x———— x, plasma protein value.

cyte count is normal and the hemoglobin concentration per milliliter is reasonably good then all is well. Some believe that the need for transfusion may be based upon the mean corpuscular hemoglobin concentration. We must reiterate that such beliefs are grossly misleading and lull one into a false sense of security. Then, when a patient dies suddenly of shock in early postoperative period many reasons are propounded, but they often do not include the most likely cause, preoperative blood volume, circulating hemoglobin, and circulating protein deficits of serious proportions.

If there be any close correlation between hemoglobin concentration per milliliter, plasma protein concentration per milliliter, hematocrit, and mean corpuscular hemoglobin concentration with total blood volume, plasma volume, total circulating hemoglobin mass, total circulating plasma proteins, and body protein deficit, then such relationship should show plainly if these values were plotted on the same graphs. In the preceding graphs, to make interpretation easier, the deficits were plotted from the greatest value at the left in descending order through the 100 cases to the lowest value at the right. As pointed out, such correlation does not exist.

It has been shown, in both dog and man, that reduction of 30 per cent of circulating blood volume may be followed by shock. Additional loss of blood during operation on a patient with a blood volume already reduced 20 per cent may precipitate shock. Evans and his associates, while investigating a series of patients with severe traumatic injuries, noted that signs of shock did not appear until the blood volume was decreased by at least 15 per cent. Severe shock in their series did not appear until the blood volume was decreased by 38 per cent of the normal expected volume. Their work agrees favorably with that done by Gregersen who found that in both dog and man an acute reduction of 30 to 40 per cent in the circulating blood volume is followed in hours by the characteristic symptoms of shock.

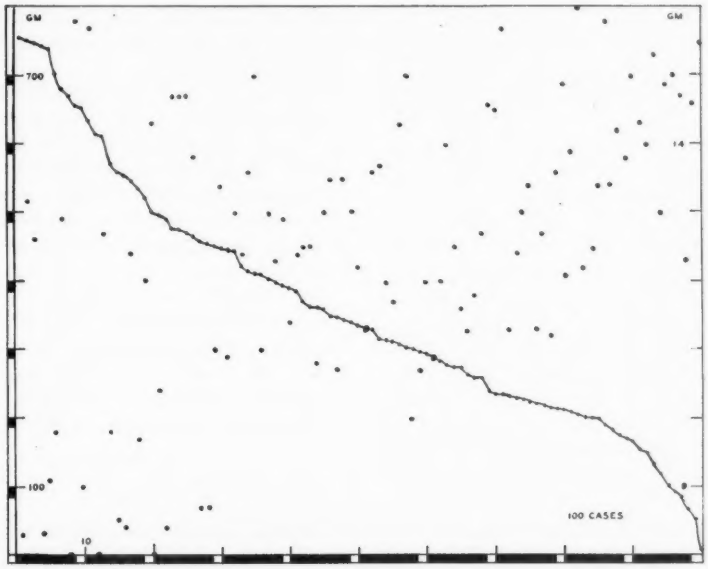

Fig. 7. When the grams of hemoglobin per 100 milliliters are plotted against the hemoglobin deficits in descending order, the tremendously wide scatter and lack of correlation between the larger deficits and the hemoglobin values is readily apparent. There seems to be more trend toward grouping in the upper right of the chart for the values corresponding to the smaller deficits. When correlation is needed the most, it is almost nonexistent. Dot indicates grams of hemoglobin per 100 milliliters; •—•—•—•—•, hemoglobin deficits.

In both these studies the reduction in blood volume was an acute process. Where, then, does the blood volume deficit become significant in chronic illness, or long standing malnutrition? Clark and his associates have shown that in states of chronic infection, carcinoma, and malnutrition in the older age group, there is a great reduction in the circulating blood volume comparable with weight loss and amounting to as much as 60 per cent.

In our series we have arbitrarily considered a deficit of 10 per cent of the normal expected blood volume to be a significant amount.

It is our opinion that a patient with a blood volume deficit of more than 500 milliliters, approximately 10 per cent of total volume, should be considered in the class of questionable risk, especially if there is a history of prolonged illness, serious shorter illness with confinement to bed or nutritional abnormalities. These, of course, usually will be reflected by deficits of hemoglobin mass, circulating proteins and body proteins. We believe that replacement is imperative if there be a blood volume deficit of 1,000 milliliters or more or when there is a 20 per cent reduction of hemoglobin mass or circulating plasma proteins. When the loss is greater than 20 per cent the patient must be considered an undesirable risk until replacement is completed before going to the operating room.

Since there is considerable variation in weight, the conversion of all deficits to values per kilogram seems to be a better basis for comparison. We have made such conversions on the basis of both present and estimated normal weight in each case. The limitations of space prevent the inclusion of the large amount of data, but it is interesting to note that there is parallelism of the per kilogram values in each category according to estimated normal weight but not to present weight, thus indicating that the estimation of normal weight in our series has been more accurate

TABLE III.—VALUES IN 100 CASES

Case No.		Blood volume ml. per kgm.	Plasma volume ml. per kgm.	Cell volume ml. per kgm.	Circulating hemoglobin ml. per kgm.	Circulating proteins ml. per kgm.
1-75	Max.	78.0	46.7	41.0	12.30	3.25
	Min.	30.5	19.3	10.5	2.46	0.78
	Mean	64.4	37.8	25.5	7.87	2.46
76-100	Max.	93.6	55.2	47.5	12.15	3.50
	Min.	53.8	26.9	24.8	4.82	2.00
	Mean	77.8	45.4	35.5	10.00	2.79
1-100	Max.	93.6	55.2	47.5	12.30	3.50
	Min.	30.5	19.3	10.5	2.46	0.78
	Mean	67.7	39.7	28.0	8.42	2.53

than reliance on present weight. Table III shows the maximum, minimum, and mean values for each in our series.

SUMMARY

Blood volume studies with determination of and replacement of deficits were performed in 100 consecutive cases of major surgery and the conclusions therefrom discussed.

An evaluation of the errors in the method and of the significance of the deficits has been made, and then correlated with assessment of operative risk.

A deficit of 10 per cent of total blood volume or of 500 milliliters or more is significant. Patients with blood volume deficits of from 500 to 1,000 milliliters should be considered questionable risks. All patients with more than 1,000 milliliters deficit must be classified as poor surgical risks, and replacement prior to operation is essential. In the former group, replacement is desirable but may be done during operation.

In judging the significance of a deficit, the amount must be correlated with the weight of the individual, a smaller deficit in a smaller person being as severe as a large one in a large person. Replacement is mandatory before operation if the blood volume is 76.5 milliliters per kilogram or less.

Ordinary laboratory determinations of hemoglobin, hematocrit, erythrocytes, and plasma proteins are usually grossly misleading and show no constant parallelism with actual total volumes. Parallelism does exist, however, between blood volume deficit and blood volume per kilogram as well as between the corresponding figures for plasma, cells, hemoglobin, and plasma protein.

Quantitative replacement of the deficient elements of the circulating blood before operation will result in reduced operative risk, lessened morbidity, lowered mortality, and widening of the scope of surgical procedures.

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BENIGN TUMORS OF BONE

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EMBRYONIC processes concerned in the formation of bone and the subsequent growth of the components of osseous tissue are important factors in determining the nature of bone tumors which may arise.

The majority of benign and malignant lesions of bone occur in endochondral bone during adolescence at or medial to the growth zone during the period of greatest bone growth activity. Embryonal processes occurring in this zone include: orderly arrangement of blastemal tissue into the pattern of subsequent skeletal structure; cartilaginous growth; calcification of cartilaginous intercellular substance; the resorption and vascularization of cartilaginous tissue leaving calcified spicules to act as a base for endosteal osteoblastic activity; ossification of endosteal spicules and periosteal fibrous tissue; subsequent growth of cortex and revascularization of early endosteal bone leading to re-formation of more permanent and useful endosteal bone.

Membranous bone results from a direct ossification of periosteal and intramembranous connective tissue through a direct transformation of fibroblast to osteoblast to osteoid tissue (certain skull bones and cortex of all bones). Both enchondral and membranous bone have a common process of ossification from this point on.

Ossification in its final formative phase utilizes a complex mineral salt composed of calcium carbonate and phosphate. The calcium salt is deposited in the osteoid tissue where bone is being formed. At the same time calcium is resorbed from other areas of bone matrix in accordance with certain physical-chemical laws and resultant osteoclastic activity. During the resorptive phase of bone growth and repair vascular tissue is found in connection with the prominent osteoclastic activity. Such lability of the osseous structure is related to changes seen in some of the benign lesions of bone.

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In the development of benign tumors of bone (Table I), (1) cartilage growth is represented by chondromas, etc.; (2) vascularization of cartilage and resorptive changes in the osseous structure are related to giant cell tumor and bone cyst; (3) ossification of membrane bone is related to osteoma, ossifying fibroma and parosteal or myo-osseous osteoma; (4) combinations of the processes above are reflected in the development of osteochondroma, chondroblastomas, etc.; (5) the marrow, vessels, supportive connective tissue and periosteal tissues give rise to benign tumors which show definite proliferative or resorptive changes in bone; (6) endocrine, renal, and other disturbances of mineral metabolism may bring about defects in bone (multiple osteitis fibrosa cystica).

Throughout life foci of potential growth persist at points where transitions of tissue are found and may be the source of neoplastic bone proliferation.

CARTILAGINOUS

Osteochondroma. This is the largest group of benign tumors arising from precartilaginous connective tissue in the skeleton. These neoplasms are most frequent near the ends of the long bones of patients between the ages of 10 and 25 years. The other sites of importance are the bones of the thoracic cage and the small bones of the foot and hand. The distinctive diagnostic features are the pedicle of normal bone protruding from the bone cortex and the rim of cartilage overlying it. A similar structure may be seen microscopically (Fig. 1b). In the x-ray picture is depicted the compact differentiated outgrowth of bone and an overlying cartilaginous cap flecked with calcium (Fig. 1a). Cases of single osteochondromas without symptoms frequently go unnoticed. They may be left untreated but must be watched by interval x-ray examination, since they may undergo secondary ma-

TABLE I.—CLASSIFICATION OF BENIGN BONE TUMORS*

Tumors of osseous origin

Cartilaginous	Osseous	Resorptive
Osteochondroma (solitary and multiple)	Osteomas and ossifying fibromas of skull and jaw	Bone cyst
		Diffuse osteitis fibrosa
Chondroma	Osteoid-osteoma	Fibrous dysplasia
Chondroblastoma benign	Parosteal ossifying fibromas	Giant cell tumor
	Recurrent myositis ossificans	

Tumors of nonosseous origin

Marrow and haversian systems	Inclusion or direct invasion
Xanthomas and granulomas	Angioma
	Lymphangioma
	Fibroma
	Neurofibroma, etc.
	Giant cell xanthoma

*After Geschickter and Copeland. *Tumors of Bone.* Philadelphia: J. B. Lippincott Co., 1949.

lignant change, particularly after the age of 30 years. Histogenetically, an exostosis represents a failure in the accurate approximation of tendon and cortex. Simple excision usually suffices to cure the osteochondromas which produce pain or dysfunction. In a large series of cases, up to 5 per cent of osteochondromas have shown malignant changes and require radical extirpation.

In hereditary or *multiple osteochondromas*, the regions most frequently and severely affected are those of the forearm (Fig. 2) and lower leg, the bones of which may be fused at one point. The prognosis as far as life is concerned is good, but there is no adequate form of treatment except operation for correction of deformities and removal of an osteochondroma causing pain or dysfunction. In a few cases with multiple skeletal involvement, secondary malignant change is observed in the cartilaginous growths, microscopically showing chondromyxosarcoma. X-ray or radium therapy plays little role in the treatment of these cases. Resection or amputation when necessary is the treatment of choice.

Chondroma. Chondroma is a common type of central cartilaginous tumor, often classified with the benign osteochondromas. It occurs most frequently in the small bones of the hands and feet, also in the spine, ribs, and sternum and, occasionally, in the long bones. In the small bones of the acra the tumor composed of radiolucent cartilage appears as a central lesion with rarefaction, visible in the roentgenogram as a cystic area, within a shell of cortical bone (Fig. 3a). Histologically, a central area of cartilage with orderly arrangement of cells and some calcification is usually seen (Fig. 3b). In some chondromas, myxoma may be present in varying amounts. The lesions are rarely multiple and occasionally affect long bones. In deciding whether a particular chondroma is to be treated from the standpoint of a benign or malignant lesion, the location and not the pathologic changes are given primary consideration. Lesions in the small bones of the hands and feet may be looked upon as benign and curable by thorough extirpation (curettement and cauterization). Only rarely has a central chondroma of the phalanges, metacarpals, or metatarsal bones shown malignant propensities. True chondromas of large size occurring about the sternum or in the long bones must be looked upon as potentially malignant. They should be removed if possible. X-ray or teleradium therapy has been of benefit in retarding the growth in a few cases.

Mafucci's syndrome or dyschondroplasia with hemangiomatosis is a nonhereditary mesodermal dysplasia. Development may be retarded on one side of the skeleton or in individual bones. Principally the bones of the extremities, thoracic cage, pelvis, and vertebrae are involved. Multiple central chondromas made up of myxoma and adult cartilage associated with soft part hemangiomas are observed. The structure of the angiomatous tumors is cavernous to cellular angioblastic in type. Deformities may appear early but become stationary in the early twenties. Trivial injuries may cause fractures through a chondromatous area. The patients present deformities. Occasionally amputation of an extremity is required because of deformity, discomfort, and loss of function.

Chondroblastoma—benign. Chondroblastoma is a rare osteolytic variant of chondroblastic tissue origin sometimes called cartilaginous giant cell tumor. It arises from a proliferation of cartilage at the epiphyseal

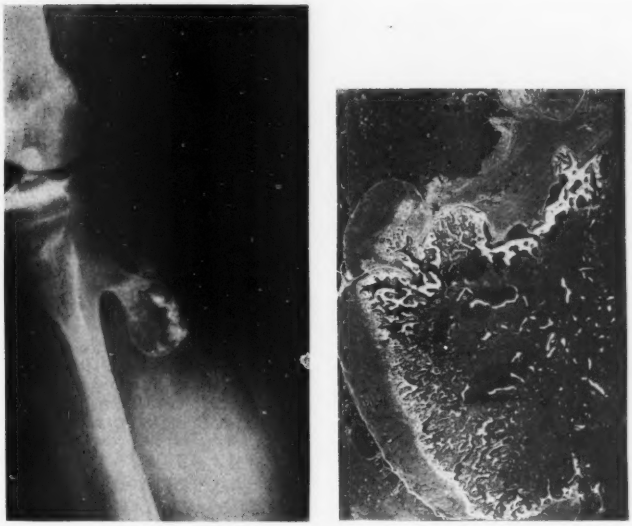


Fig. 1. a, left, Osteochondroma of pedicle type at the upper end of the tibia, posterior. Note the widened metaphyseal region near the lesion, and the extension of the pedicle in the direction of the pull of the extensor muscles. b, Low power photomicrograph of benign osteochondroma. Cartilaginous cap is seen overlapping the zone of cancellous bone, inclosing areas of fatty bone marrow.

line, usually between the ages of 10 and 20 years. It is most frequently found about the upper end of the tibia, lower end of the femur, and upper end of the humerus. Symptoms of pain, tumor, and dysfunction prior to operation, average 5 months.

In the x-ray picture there is a characteristic mottled, cystic area of bone destruction, with expansion of the bone shell and usually some periosteal reaction (Fig. 4a). Not infrequently the tumor bears a marked similarity to giant cell tumor. Microscopically, one sees masses of young and adult cartilage with areas of uncalcified matrix. The tumor has areas of marked vascularity. Near the vascular areas and about the periphery of the cartilage, numerous giant cell osteoclasts are seen (Fig. 4b).

Some of these tumors may show malignant degeneration which frequently cannot be differentiated from the benign lesions except by histopathological study. Many investigators separate the benign tumors from the malignant variety, placing the latter with the chondrosarcoma group.

Though the benign chondroblastoma is not radiosensitive, radium or x-ray therapy (Cou-

Fig. 2. Roentgenogram of radius and ulna in a case of multiple osteochondromatosis. Note the bending and distortion of bones of the forearm and the undeveloped state of the distal end of the ulna.

Fig. 3 a.

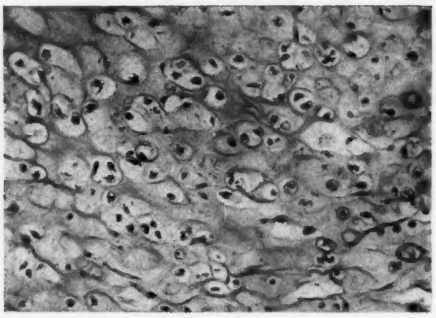


Fig. 3 b.

Fig. 3. a, Roentgenogram depicting a central chondroma situated in the middle phalanx of the little finger. Note the central zone of rarefaction surrounded by a thin bone cell. b, Photomicrograph of the tissue removed from this lesion, showing cartilage with orderly arrangement of cells and tendency to calcification.

tard method) in the benign lesions, following exploration and curettage, is recommended, unless the tumor occurs in a bone which can be resected without sacrifice of function. The malignant variety of chondroblastoma has been uniformly fatal despite primary amputation.

OSSEOUS

Osteoma and ossifying fibromas. These growths are due to direct ossification in fibrous tissue. They usually occur in children or young adults in the frontal or parietal bones of the skull, in the bony walls of the frontal or maxillary sinuses, and in the mandible. They are much more rare than are osteochondromas. The more rapidly growing osteomas are composed of cellular fibrous tissue in which small, round osteoid bodies are formed. The more

Fig. 4 a.

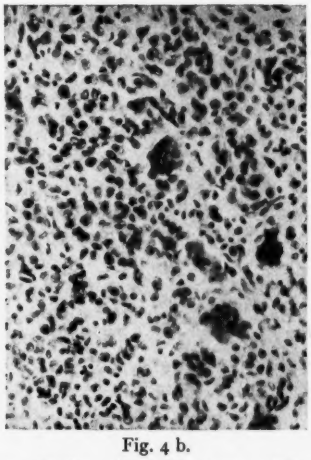


Fig. 4 b.

Fig. 4. a, Benign chondroblastoma with radiologic changes in the lower femur, showing areas of cystic destruction, trabeculation and some periosteal reaction. The defect is situated principally on the metaphyseal side of the bone. b, Photomicrograph of lesion shown in a, in which masses of young cartilage cells are seen with typical osteoclasts present in the tissue. These giant cells are usually seen at the periphery of the cartilage or near vascular areas.

Fig. 5 a.

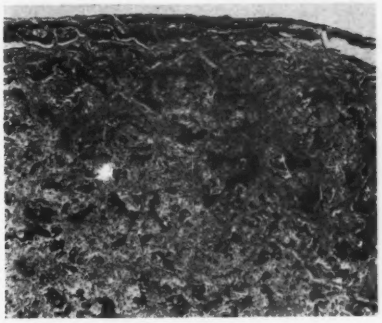


Fig. 5 b.

Fig. 5. a, Gross specimen removed from the region of the antrum in a patient suffering from ossifying fibroma. b, Photograph of ossifying fibroma showing cellular character of fibrous stroma and irregular ossified bodies.

slowly growing tumors of this type form spongy bone and sometimes ultimately give rise to compact bone, frequently referred to as eburnated osteomas (Fig. 5a and b). The roentgenographic findings show a dense mass of new bone, smoothly outlined, with a sharply demarcated base formed by the thickened, slightly depressed inner table of the skull. When seen in the mandible, the roentgenogram reveals a tumor mass of regular contour projecting from the normal bony structure. The new bone is less dense than the normal bone. In the region of the antrum, the affected side shows increased density or cloudiness. In most instances, the tumor arises outside the antrum and encroaches upon the antral cavity, or pushes downward toward the alveolar border, displacing the teeth downward.

These lesions are often complicated by trauma or infection.

Osteoma and ossifying fibromas are benign tumors and do not warrant radical or mutilating operations. It has been found that simple excision usually suffices to eradicate the disease.

Fig. 6 a.

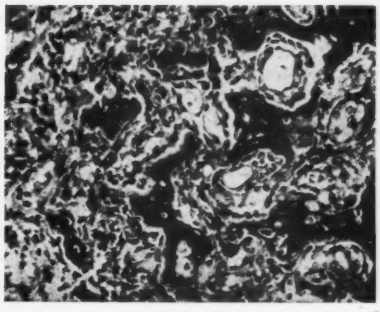


Fig. 6 b.

Fig. 6. a, Roentgenogram of osteoid osteoma showing an area of intracortical sclerosis with indistinct area of rarefaction. This lesion may be confused with sclerosing periosteitis when the reactive sclerotic area far exceeds the radiolucent area as in this case. b, The photomicrograph of the central lesion reveals osteoid spicules developing in the proliferating endosteal tissue.

Fig. 7. Roentgenogram of a parosteal osteoma situated at the lower end of the femur. The lesion appears discrete and separate from the femur in this view, but the anterior posterior view indicated that a portion of the lesion is involving the adjacent femur.

Osteoid-osteoma. Osteoid-osteoma is a small, rarefying lesion found in enchondral bone which is composed of vascular fibrous tissue and proliferating fibroblasts in which trabeculae of newly formed osseous tissue are noted (Fig. 6b). The lesion usually does not exceed a centimeter in diameter. The patients are usually young adults or adolescents. Localized pain is often the primary complaint and may be associated with tenderness without fever or leucocytosis. The lesion is chronic and may persist for a period of months to 1 or more years. In the roentgenogram, a dense, sclerosing, opaque zone about a small oval or rounded area of rarefaction is seen (Fig. 6a). It may occur either as an intracortical lesion or in the cancellous portions of the bone. It is found in bones of the hands, feet, vertebrae, or shafts of the long bones.

The two principal theories on the nature of osteoid osteoma at this time support the contention (1) that the lesion is a primary neoplastic process of bone, and (2) that the process is inflammatory in origin. Another unverified interpretation holds that the osteoid-osteoma represents a healing area about a bone infarction of minute size.

Excision will cure these small, benign lesions.

Parosteal ossifying fibroma or myo-osseous osteoma. Parosteal osteoma is a rare lesion composed of ossifying fibrous tissue, suggesting a circumscribed myositis ossificans. It differs, however, in that it involves the neighboring bone in many instances, though it may be confined entirely to the soft parts. The roentgenogram reveals an ossifying mass, usually of considerable size, extending out into the soft parts with or without intimate connection to the neighboring bone (Fig. 7). A common site is the region of the lower femur. Microscopically, the lesion suggests a cellular myositis ossificans, with bony trabeculae imbedded in fibrous tissue. The fibroblasts, osteoblasts, and giant cells may be intermingled in areas which suggest osteolytic sarcoma. Close observation of the nuclei, however, reveal the lesion to be benign. The tumor grows at a slow rate, giving rise to symptoms of tenderness, pain, and ultimate dysfunction. A palpable lump is felt as one of the early manifestations of the disease. In rare instances malignant changes in the tumor may supervene.

Excision is the treatment of choice. When the neighboring bone is invaded, even if the benign character of the tissue is confirmed by microscopic examination, x-ray therapy should be given postoperatively. If renewed growth is seen, amputation must be performed because of the potential malignant change present in this condition.

Recurrent myositis ossificans. This condition may be divided into the traumatic and atraumatic forms arising about the thigh, arm, elbow, neck, and lumbar muscles. Occupation plays little or no role in the case histories studied. Injury is definitely an important factor in 60 per cent of the lesions. The age incidence varies between 10 and 72 years. The earliest physical sign after injury is the development of a soft, compressible mass which soon becomes indurated. Bone may be detected in the roentgenogram within 3 weeks after the onset of the tumor formation. Small dense areas of calcification soon assume large

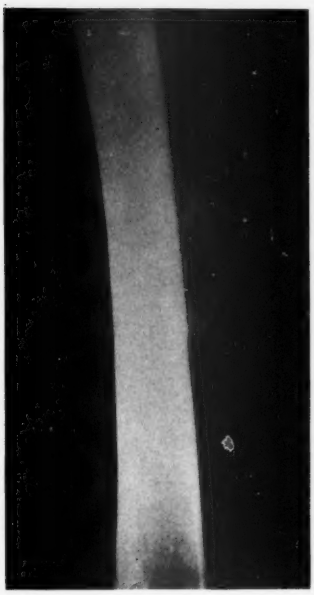


Fig. 8 a.

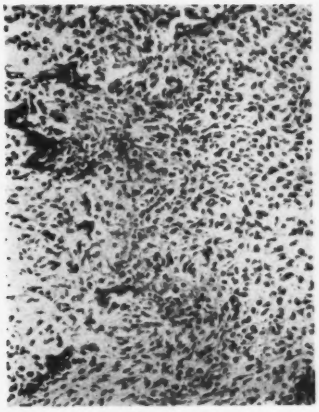


Fig. 8 b.

Fig. 8. a, Roentgenogram showing myositis ossificans. Note the typical laminated structure of the bone deposits in the soft part about the femur. b, Photomicrograph depicting development of osteoid tissue in myositis ossificans, with proliferation of osteoblasts and calcification. Cartilage cells are present. This represents an advanced phase of the disease.

proportions forming a large spicule of bone, usually separated from the shaft of the neighboring bone (Fig. 8a). Many lesions gain their maximum growth in 6 weeks or more, and then, spontaneously, regression is followed by quiescence. Histologically, degeneration of muscle, hyperplasia of connective tissue, and organization of hemorrhage are early findings. Osteoid tissue with marrow spaces, osteoblasts about the spicules of bone, occasional islands of cartilage (30 per cent of cases), and benign myxomatous tissue represent fully developed myositis ossificans (Fig. 8b).

A conservative form of treatment is desirable in the majority of cases and the lesion may be watched, without treatment, by interval x-ray examination. Postoperative recurrences are frequent if surgical removal is employed too early (under 6 months), or if excision is inadequate. There are isolated cases which have shown successful regression of a recurrence following x-ray therapy. Insufficient experience with the use of irradiation for the treatment of myositis ossificans prevents any final evaluation of this mode of therapy.

Of 22 cases studied, 2 patients have shown malignant changes in the area of myositis ossificans, 1 in the deltoid and 1 in the gastrocnemius muscles.

Myositis ossificans progressiva is a special form of the malady, which usually begins in childhood, affecting the spinal muscles, primarily. As the name implies, it eventually involves the muscles of the entire skeletal system. Conservative therapy only is indicated. The ultimate outcome is usually fatal.

RESORPTIVE

Bone cyst. The benign solitary bone cyst is frequent in children under the age of 18 years. It usually occurs in the shaft near the upper ends of the humerus, femur, or tibia and runs a protracted and benign course (Fig. 9a). Pathologic fracture is the only acute phase of the disease and probably the most frequent reason for consulting a physician. The x-ray picture shows a central expanded bone defect, symmetrical and regular in contour. Microscopically, a healing bone reaction is noted about the cavity which may be lined by fibrous tissue (Fig. 9b). It usually is filled with straw colored fluid or remains of old hemorrhage. Some cysts are trabeculated. Spontaneous

Fig. 9 a.

Fig. 9 b.

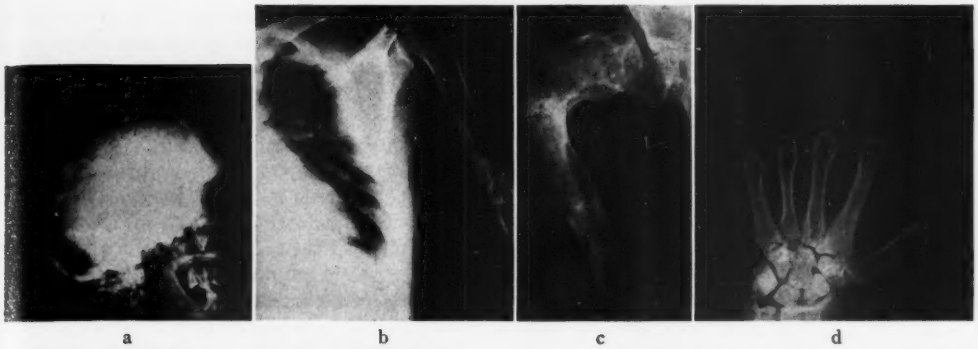
Fig. 9. a, X-ray picture showing a bone cyst in the shaft of the upper end of the humerus. Note the lesion is centrally located, surrounded by a thin bone shell, and that it is situated near the epiphysis. b, Microscopically, a healing bone reaction is noted about the cavity of the cyst, with osteoblastic proliferation and formation of bone spicules. There is some vascularity present with an occasional osteoclast.

arrest of the lesion without obliteration of the cavity results in the latent bone cyst. Fracture through the cyst may result in healing. Variations of the simple bone cyst may be encountered:

1. Giant cell variant of the bone cyst, in which the duration of symptoms is found to be shorter and in which the lesion is located invariably near the epiphysis of the bone on the metaphyseal side. This variant is most commonly found in the greater trochanter of the femur and lower radius. In the roentgenogram it is polycystic in character, more subcortical than central, and most frequently trabeculated. Microscopically, the walls are lined by fibrous stroma containing variable numbers of giant cells. Hemorrhage occurs frequently. These lesions stand midway between the typical bone cyst and giant cell tumor.

2. Polycystic osteitis fibrosa, a multilocular structure, occurs either as a single lesion or with generalized osteitis fibrosa cystica. The cysts occur near the epiphysis on the metaphyseal side, but extend over a considerable area of the bone shaft. The duration of symptoms averages about 5 months. In the roentgenogram they appear as an aggregation of small cysts, which have more or less coalesced, giving a polycystic appearance with some expansion of the cortex. Histologically, there are many small cysts, usually filled with blood and surrounded by giant cells. Varying amounts of fibrous tissue may be seen.

The prognosis as to life is good in these forms of bone cysts. In the solitary bone cyst of the adult in which symptoms are absent, no treatment is indicated. In the solitary bone cyst of young people, in which fracture has occurred and the position of the fragments is satisfactory, simple fixation usually gives a good result. If the lesion is progressive after several months, exploration and curettement, followed by chemical cauterization, are indicated. Bone chips or crushing of the bone shell



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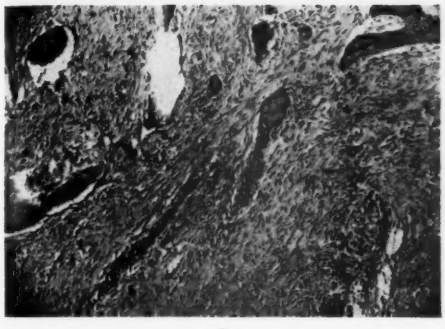

e

Fig. 10. X-ray studies of patient with polyostotic fibrous dysplasia. a, Note the dense and hyperostotic changes in the base of the skull (important differential point from hyperparathyroidism). b, Roentgenographic changes are seen in the upper humerus with an associated fracture. There is rarefaction with cyst formation, and some expansion of the mid and lower portions of the shaft. c, Roentgenogram of femur showing a ("shepherd's crook") deformity of the upper portion of the bone, with expansion, multiple cyst formation, and trabeculation throughout the shaft. d, Roentgenogram revealing sclerotic changes in the bones of the hand, especially the second metacarpal. e, Microscopically, the cancellous bone and marrow are shown to be replaced by resilient, yellow-white connective tissue, with varying numbers of small cysts. Trabeculae are noted in the periphery, partly calcified or composed of newly formed bone.

may be used to obliterate the cavity. In the acute bone cyst (giant cell variant) moderate amounts of x-ray therapy given in divided doses are adequate treatment if the diagnosis is certain. Should irradiation fail, operative interference may be necessary. Primary curettement and cauterization yield excellent results. Irradiation followed by surgical procedures gives less satisfactory healing in the aggressive bone cysts.

3. Multiple osteitis fibrosa cystica is a generalized demineralization of bones due to hyperparathyroidism. Bone involvement is most pronounced in the pelvis, spine, and long bones. The calcium in the serum may or may not be elevated. This disease occurs at any age from childhood to late adult life. The depletion of calcium and phosphorus results in definite rarefaction of the bones with bending deformity and definite cystic lesions, any one of which may be associated with spontaneous fracture. Less commonly seen is collapse of the vertebrae and other skeletal disturbances. Urinary calculi commonly develop, leading to renal colic and hematuria. The blood serum calcium varies from 12 to as high as 23 milligrams per 100 cubic centimeters, while the plasma phosphorus may be depressed as low as 1 or 2 milligrams per 100 cubic centimeters of blood. The endocrine basis for the various changes seen in this disease have been well substantiated. Parathyroid adenomas are being demonstrated in increasing numbers of cases. In the differential diagnosis of osteitis fibrosa cystica generalisata, fibrous dysplasia, multiple myeloma, and metastatic carcinoma are to be considered. The roentgenograms reveal multiple cysts with or without diffuse rarefaction or bending deformities. In those lesions which have been biopsied, the microscopic structure varies depending on the activity of the disease. The aggressive phase of osteitis fibrosa is characterized by tissue typical of giant cell tumor, while in the chronic state, the sections reveal tissue characteristic of the healing reaction about bone cysts.

Fig. 11. Roentgenogram showing monostotic fibrous dysplasia in the upper end of the femur, with fracture. Note the cortical location, with rarefaction and the evidence of formation of many small cysts.

The treatment is directed toward the underlying cause of the condition, i.e., hyperplasia or adenoma in the parathyroid glands. After the diagnosis is established, the parathyroid glands should be explored. It is to be remembered that some parathyroid adenomas have been found within the upper chest cavity.

Fibrous dysplasia. There are two forms of fibrous dysplasia—the diffuse or polyostotic form, and the monostotic form.

In the diffuse or multiple form of fibrous dysplasia, the disease involves multiple bones on one side of the body. Occasionally, there is a bilateral disturbance. Albright and his coworkers have emphasized the extraskeletal features of the disease, which include pigmentation of the skin and endocrine dysfunction in girls, in the form of sexual precocity and hyperthyroidism. These manifestations are not present in all cases. On roentgenographic examination, the bones are bowed and rarefied, with thinning and expansion of the cortex. Pathological fractures occur (Fig. 10a, b, c, d). The pathological changes show the interior of the bone to be replaced by fibrous tissue of a gray or yellowish color which may contain islands of calcification, cartilage, ossified bone or small cysts (Fig. 10e).

In monostotic fibrous dysplasia, the first evidence of the disease is usually a local swelling with an occasional tenderness or pain of an arthritic character. Pathologic fracture may be the first sign of the disease. The lesion appears either to grow slowly or to remain stationary. Cutaneous and endocrine abnor-

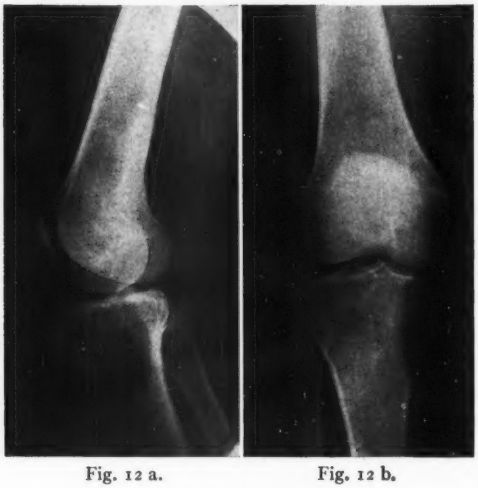

Fig. 12 a. Fig. 12 b.

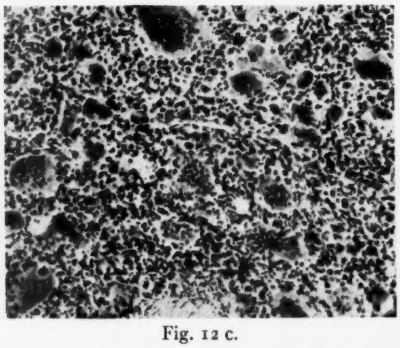

Fig. 12 c.

Fig. 12. a and b, Roentgenographic study of the upper end of the tibia, showing unilateral metaphyseal lesion typical of early giant cell tumor. Note the area of destruction with trabeculation and the lack of periosteal reaction. c, Photomicrograph revealing typical tissue from the giant cell tumor. Note many giant cells, containing 15 or more nuclei, and stroma composed of round and spindle cells.

malities are lacking. The flat as well as the long bones may be affected. The roentgenogram shows, in the long bones, an area of radiolucence, sometimes traversed by delicate trabeculae of bone (Fig. 11). These may be centrally placed or eccentrically located, especially in the metaphyseal area of the long bones.

Fibrous dysplasia is apparently a true dystrophy in which the tendency to normal ossification is prevented by a fundamental local disturbance yet to be demonstrated.

It is usually recognized at the beginning of the second decade, though most often it comes under observation in the third decade. It appears to be a chronic process persistent throughout life.

Surgical excision is justified in lesions that give rise to symptoms or interfere with functional activity. Resection or thorough curetting should be resorted to; incomplete removal leads to recrudescence of the process. Irradiation is without benefit.

Benign giant cell tumor. This is an epiphyseal lesion which occurs after the age of 18 years. It is most frequent in the lower end of the femur, upper end of the tibia, and lower end of the radius. The duration of symptoms averages 14 months. The sequence of events is trauma, pain, tumor, and, occasionally, pathologic fracture. In the roentgenograms an early giant cell tumor shows a defect situated asymmetrically in an epiphysis, later in the disease extending to a more central position. The defect is surrounded by a bone shell which may be perforated. The lesion is progressive (Fig. 12a and b). Microscopically, the tumor is composed of large giant cells, embedded in a mass of typical small round cells (Fig. 12c). There are a number of variants of giant cell tumor. Certain lesions of sesamoid bones, the jaws, and about the teeth, are related pathologically to giant cell tumor.

Conservatism in the treatment of giant cell tumor has been in vogue since 1912. If one has to consider the economy of the time for convalescence, surgery is the procedure of choice. In all lesions biopsies should be made. In a primary case, not too advanced, curettement followed by cauterization is advocated, especially in the lower femur and the upper tibia. In advanced lesions of the ulna, fibula, or radius, resection should be used. Recurrences following curettement may be troublesome and call for further curettement or even resection when possible. An uncontrolled giant cell tumor is usually due to incomplete removal, perforation of the bone shell, or declining reaction of the bone cortex due to age. Many giant cell tumors are radiosensitive but the mechanism of response is not well understood. Opinion varies greatly on the efficacy of irradiation versus surgical intervention in benign giant cell tumor. It is well established

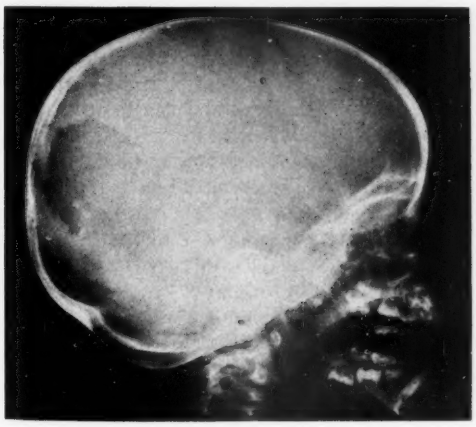

Fig. 13 a.

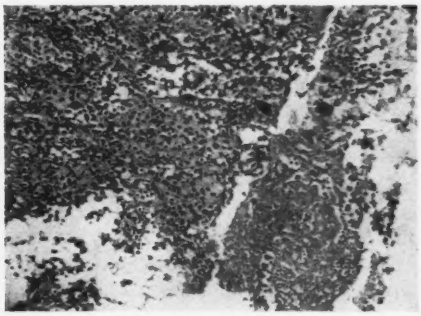

Fig. 13 b.

Fig. 13. a, Roentgenogram of a patient's skull showing an area of rarefaction in the occipitoparietal region, typical of Christian-Schueller's disease. Note the large area which is definitely demarcated. b, Photomicrograph from a lesion of Christian-Schueller's disease, showing foreign body giant cells, foam cells, blood pigment, and many macrophages.

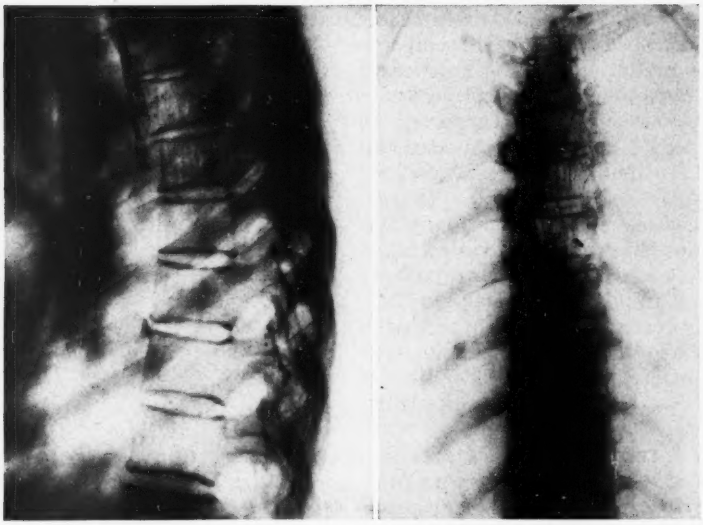

Fig. 14. a, left, and b, Two views of angioma involving multiple vertebrae. Note the striated trabeculations with rarefaction, giving the bones a definitely porous appearance. No periosteal reaction is noted. Expansion of the bone shell is noted, especially present in long bones when involved.

that certain lesions irradiated alone or treated by surgery alone heal perfectly, but the combination of the two forms of therapy may give many unfortunate results. Treatment by irradiation is less favorable in the weight-bearing bones than in other locations. Many giant cell tumors are inoperable from the standpoint of preserving function because of their location or extent, but may be successfully treated with x-ray therapy. Irradiation, by fractionated dosage, given with sufficient intervals of time, is an important factor in avoiding deformity and other complications. A small percentage (1 to 2 per cent) of giant cell tumors undergo malignant change. In nearly every case when this is found, prolonged and ill-advised irradiation has been given. The microscopic differentiation between osteolytic sarcoma and benign giant cell tumor is difficult at times and adds to the number of cases in which sarcoma is discovered late in the disease.

MARROW AND HAVERSIAN SYSTEMS

This group of bone lesions is often associated with disturbances in lipoid metabolism. Organs connected with the reticuloendothelial system reveal a variety of granulomatous lesions.

There appears to be a close relationship between Letterer-Siwe's disease, Hand-Schueller-Christian's disease and eosinophilic granuloma. Further, it seems logical to assume that they represent gradations of disturbance in lipoid metabolism and in the reticuloendothelial system.

Letterer-Siwe's disease. This nonlipoid histiocytosis is a rapidly fatal disease of infancy, and will not be discussed.

Hand-Schueller-Christian's disease. The disease usually makes its appearance in late infancy and is rarely seen after childhood. The clinical manifestations are variable. Exophthalmus, diabetes insipidus, pigmentation of the skin and splenomegaly may be seen. Bone changes are a constant finding and roentgenographically appear as large, rarefied defects, clearly demarcated in the skull (Fig. 13a) and in other flat bones. Diffuse cystic areas may also be seen in the long bones with thinning of the cortex. There is no periosteal reaction. The blood picture may show a severe anemia. Histologically, large macrocytes, often binucleated, are the characteristic cells together with eosinophils, plasma cells, and lymphocytes (Fig. 13b). The lesions are quite radio-

Fig. 15 a.

Fig. 15 b.

Fig. 15. a, Case of Dr. W. H. Bickle. Roentgenogram depicting multiple bone involvement of lymphangioma. Note the cystic rarefaction and deformity of the coccyx; also the cystic changes in the lumbar vertebrae. The femurs and pelvis were also involved in this patient. b, Photomicrograph of biopsy taken from this patient reveals large dilated lymphatic channels with foci of perilymphatic lymphoid tissue about the area. The lymphangioma invaded muscle attachments as well as the bone.

sensitive and the affected bones often reossify under x-ray therapy. Great care must be exercised in giving the treatment to prevent overwhelming anemia. Transfusions are frequently indicated during the period of active roentgen therapy. Small divided doses are best tolerated. Many of these patients survive for an indefinite time with relative quiescence of the disease as they grow older.

Eosinophilic granuloma. Eosinophilic granuloma occurs in children and young adults. It is a relatively benign lesion arising in the medullary cavity, though often it may appear in multiple bones. A complete skeletal survey in all patients will probably reveal that it is a multiple lesion of the bones in most of the cases. The symptoms are unreliable, though pain, swelling, and dysfunction are frequently observed. A mild leucocytosis and mild eosinophilia are usually present. Radiologically the lesions in the bones are central. Osteolytic and irregular defects are observed to be quite well circumscribed or punched out. The cortex may be expanded or perforated. Histologically, the lesions show sheets of eosinophils with varying degrees of fibrosis and histiocytes interspersed through the lesion. Surgical excision or curettage promotes healing. Mild x-ray therapy also will control the disease. Spontaneous healing is rare.

BONE INVOLVEMENT BY INCLUSION OR DIRECT INVASION

Angioma of the bone is considered rare. These growths appear between the ages of 4 and 40 years but angioma is most frequent among young adults. Such tumors have been found in the humerus, ulna, radius, femur, os calcis, skull, and vertebrae. The roentgenographic picture in the long bones is one closely resembling giant cell tumor or polycystic disease of the bone, with isolated cysts beyond the main point of destruction. In addition, however, one may see changes in the vertebrae characterized by linear trabeculations, rare-

Fig. 16. Roentgenogram showing a right lateral scoliosis of the vertebrae in upper dorsal region, due to neurofibromatosis of the spinal nerve roots. The vertebrae are wedge-shaped as a result of bone destruction. The ribs in the vicinity show multiple areas of rarefaction due to changes in pressure.

faction and, occasionally, cystic destruction (Fig. 14a and b). The trabeculae traversing the cystic cavities vary in density, more so than in giant cell tumor. The lesions at exploration show cystic destruction, with or without vascular tissue, beneath a thin wall of cortical bone. The cysts contain fluid, as a rule. The vascular tissue obtained is characteristic of angiomatous tissue elsewhere. On reviewing the literature, one gains the impression that the majority of the angiomas of bone are of the cavernous type. In our cases, many showed the capillary type of angioma and 2 had proliferative changes suggestive of malignant change.

Angiomas affecting bone are essentially benign. They show varying degrees of radiosensitivity and the younger the patient the more effective the irradiation. This factor is also present in angiomas found in other parts of the body.

Lymphangioma. Occasionally lymphangioma is noted involving one or more bones with changes much like those seen in angioma. In 1 case, marked resorption of bone structure was observed in the right ischium, ilium, the sacrum, lumbar vertebrae and right femur (Fig. 15a). The surrounding soft parts showed invasion by the process. Microscopically, lymphangiomatous channels were noted, some of which were quite dilated. The lymphangiomatous tissue was associated with accumulations of lymphocytes and perilymphatic lymphoid tissue. The bone surrounding resorption areas revealed little evidence of osteoblastic activity (Fig. 15b). The treatment is largely limited to x-ray therapy.

Fibroma. Benign, nonosteogenic fibroma, as an inclusion in bone, is occasionally seen and may be confused with fibrosarcoma of bone. Roentgenographically, in the early stages it appears as a subcortical lesion with circumscribed rarefaction suggesting polycystic changes. There is, usually, no periosteal reaction. Later in the disease, by growth and pressure atrophy, the process may extend across the shaft of the bone. Most of the recognized cases have been in the shaft of the long bones.

One extensive lesion was observed in the lower end of the femur of a white woman, 29 years. The condyles of the femur were largely destroyed and an extensive soft part shadow was present. On amputating the leg, the gross specimen showed an extensive fibroid tumor, well encapsulated, but invading bone by pressure necrosis. Microscopic study revealed connective tissue proliferation resembling a benign fibroma.

In the early lesions, excision is the treatment of choice. Curettement may be carried out in selected cases. All tissue should be studied to rule out sarcomatous change in the fibrous tissue. The prognosis and treatment in these cases depend upon an accurate microscopic analysis and, secondarily, upon the degree of bone invasion.

Neurofibromatosis. Changes in the bone have been observed in cases of neurofibromatosis including: scoliosis, abnormality of growth, irregularity of outline, central and subperiosteal cysts, pedunculated subperiosteal tumors and pseudoarthrosis. The bone is involved by direct pressure from erosion and the defects in roentgenograms are usually characterized by erosion and thinning of the

Fig. 17 a.

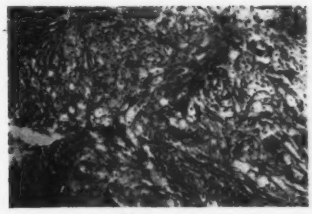

Fig. 17 b.

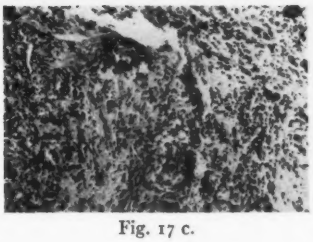

Fig. 17 c.

Fig. 17. a, Case of Dr. Jesse Nicholson, Philadelphia. Roentgenogram showing benign xanthoma, involving the distal end of the first metatarsal bone and proximal end of the phalanx, which arose primarily in the synovium of the joint. b and c, Microscopically, xanthoma cells are seen intermingled with proliferating fibrous tissue. There is more vascular tissue, with associated giant cells. Histologically, the synovial tumors grade imperceptibly into the group of giant cell tumors of the tendon sheaths.

cortex. The vertebrae are frequently involved in association with neurofibromas of the spinal nerves. Camp has made the observation that as high as 23 per cent of all tumors of the spinal cord seen at operation were neurofibromas and that 42 per cent of such cases showed changes in the vertebrae (Fig. 16).

The incidence of malignant changes in neurofibromatosis is difficult to ascertain, though available statistics indicate that a definite percentage of neurogenic sarcoma is associated with neurofibromatosis. Geschickter and Copeland have 15 patients in which the malignant tumors of nerve sheath origin were invading bone.

The treatment of the benign lesions includes excision of the neurofibroma, with correction of bone deformity, if present. Many defects will not be amenable to treatment because of the extensive changes which may be present as, for example, in the spine.

Giant cell xanthoma. Excepting benign cartilaginous tumors of the synovium, the majority of such benign lesions are characterized histopathologically by giant cell proliferation, accumulation of foam cells (xanthoma cells) and connective tissue derived from the synovial membrane. Some of these synovial tumors are characteristically of the giant cell tumor type (predominantly benign) and show a tendency to involve neighboring bone. Most of the lesions show an intermingling of giant cells, xanthoma cells, and synovial tissue. The giant cell xanthomas of the joint synovium are histologically similar to giant cell tumors of tendon sheaths.

Of 9 patients studied with giant cell xanthoma and fibroxanthoma with giant cells about the joints, 5 of the 9 patients had associated bone involvement of (1) tibia and astragalus, (2 and 3) femur and tibia, (4) humerus and olecranon of ulna, and (5) first metacarpal and adjacent phalanx (Fig. 17 a, b, c). Over 100 instances of benign giant cell xanthoma and benign synovioma of the tendon sheaths were studied by Geschickter and Copeland, and only in 1 tumor was malignant change noted. In no case had the bone been involved.

Radical excision may be resorted to in the treatment of these tumors but, if recurrence supervenes, a resection of the joint and affected soft parts usually suffices to eradicate the disease.

The small and miscellaneous group of benign tumors which have been described as nonosseous in origin yet involving bone have been gleaned from a much larger group of neoplasms, primary in bone. The initial diagnosis was usually incorrect and, frequently, after pathological examination the true nature of the lesion was missed. From the study

made by Geschickter and Copeland it is self-evident that each entity warrants careful diagnosis with individual treatment.

SUMMARY

Benign tumors of bone cover a variety of entities. They include certain true bone neoplasms, lesions of the marrow and a variety of tumors found in the bone through inclusion or invasion. The natural history of individual tumor processes indicates the care in diagnosis and treatment which should be exercised. No tumor process in bone can be considered innoxious until adequately removed and studied under the microscope. There is a definite chance that malignant metaplasia may be present in any tumor though, statistically, one may be guided toward more conservative therapy if the diagnosis is accurately known. A survey has been given of the majority of benign tumors involving bone, including pertinent findings and the general form of treatment to be used.

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THE MUCOSA AND SKIN SAVING TECHNIQUE OF HEMORRHOIDECTOMY

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THE complete relief of hemorrhoids involves the excision of the varicosities of the hemorrhoidal venous plexus. The operation should include the extirpation of all the redundant mucosa and skin. The removal of an excessive amount of epithelium, however, may result in an anal stricture or other complication outweighing the severity of the original disease. Incomplete removal of the varicose veins will result in a recurrence of the hemorrhoids.

The precise surgical technique herein described has been performed on approximately 1,000 patients during the past 12 years and has been found to meet the requirements of adequate removal of veins with conservation of sufficient mucosa and skin to prevent stricture. The operative technique is best described in connection with the illustrations.

INITIAL EXAMINATION OF THE PATIENT

The patient is first seen in the outpatient department where a complete history is taken, a physical examination is performed, and the routine laboratory work (hemoglobin and urinalysis) is done. A digital rectal and anoscopic examination is performed. If the symptoms or routine examination suggest more serious disease, such as carcinoma of the colon, the patient is given a cleansing enema and a sigmoidoscopic examination is done followed by a barium enema with fluoroscopic study by the radiologist. Roentgenograms of the barium filled colon and an evacuation film are made.

The patient is hospitalized the evening before the operation is to be done. He is seen by the anesthesiologist soon after admission and the type of anesthesia to be employed is discussed with him.

The usual preoperative orders are:

1. Shave the perineum the evening before operation.
2. Administer soapsuds enema the night before operation.
3. Give seconal 100 milligrams (1½ gr.) at bedtime and 1½ hours before operation.
4. Omit breakfast the morning of operation.
5. Give morphine sulfate 10 milligrams (⅙ gr.), 1 hour preoperative; scopolamine 0.3 milligram (1/200 gr.), 1 hour preoperative.

TYPE OF ANESTHESIA

Complete muscular relaxation is required for this operation. While the type of anesthesia to be employed is decided by the anesthesiologist, as a rule spinal anesthesia, using the saddle-block technique is preferred. Pontocaine 4 to 6 milligrams is given in 5 per cent dextrose solution. After the anesthesia has become effective the patient is placed in the lithotomy position and the perineum is prepared by washing with tincture of green soap and sterile water, and painting with tincture of zephiran solution.

THE OPERATION

The details of the operation are illustrated. The operative technique is a precise one, requiring more attention to detail than many larger operative procedures, but the results are

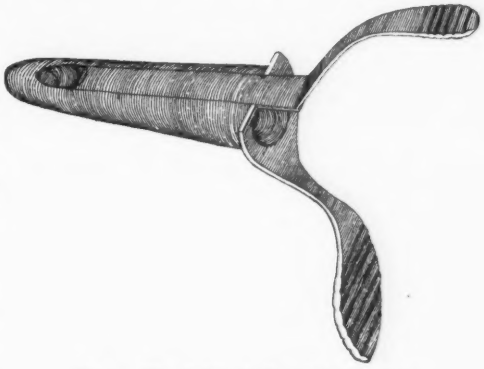

Fig. 1. The Brinkerhoff rectal speculum.

From the Department of Surgery, The Myers Clinic Hospital, Philippi, West Virginia.

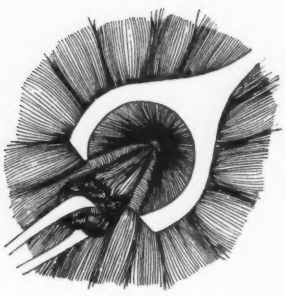

Fig. 2a.

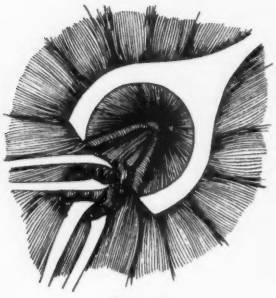

Fig. 2b.

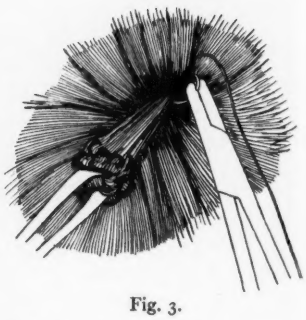

Fig. 3.

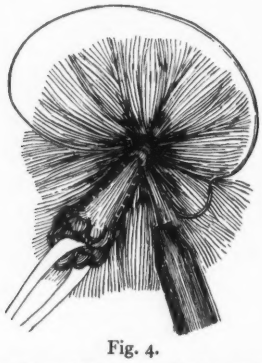

Fig. 4.

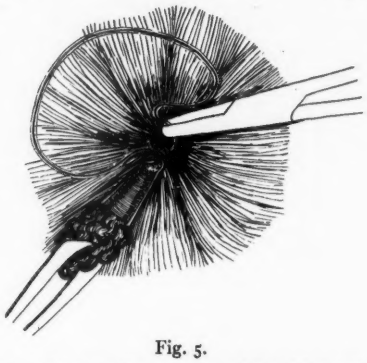

Fig. 5.

Fig. 2. a, After the saddle-block spinal anesthesia has become effective the patient is placed in lithotomy position. Another digital rectal examination is performed; then anoscopic examination using a Brinkerhoff speculum. There are usually 3 primary hemorrhoidal masses located, with the patient in the lithotomy position, at 7:30, 10:30, and 3:00 o'clock. The removal of each of these three primary hemorrhoids proceeds as follows: the internal hemorrhoid is visualized and the corresponding external hemorrhoid or skin is grasped with an Allis clamp and traction is exerted on the external hemorrhoid. b, With the Brinkerhoff rectal speculum in place and while traction is being made on the external hemorrhoid, the internal hemorrhoid is visualized and firmly grasped with a second Allis clamp. The rectal speculum is then removed.

Fig. 3. With traction being exerted on the internal hemorrhoid by means of the Allis clamp, the pedicle of the internal hemorrhoid is exposed and doubly suture-ligated with No. 0 chromic catgut on an atraumatic needle. Especial attention must be paid to this step because the hemorrhoidal pedicle contains large branches of the superior hemorrhoidal vein which will bleed profusely if the ligature is not secure.

Fig. 4. By the use of the electrosurgical knife the mucosa of the internal hemorrhoid is incised as indicated by the dotted line. The superior pole of the hemorrhoid is transected about 1 centimeter distal to the ligature. The dissection is carried down to the sphincter ani externus muscle. Varicose veins beneath the mucosa on either side of the excised mass are excised by retracting the mucosa and continuing the dissection with the electrosurgical knife. The excision is carried forward to the external hemorrhoid. Bleeding points are clamped and ligated. The Allis clamp is removed from the external hemorrhoid.

Fig. 5. The needle bearing the No. 0 chromic catgut suture is then used to transfix the previously ligated stump as shown. This is to prevent the previously placed suture-ligature from slipping off.

worth the effort of developing the skill required. Special features to be emphasized are: transfixion ligature of the superior pole of the internal hemorrhoid; conservation of mucosa and skin; complete excision of the varicosities; control of bleeding points by ligatures; and suture of mucosa only. The high frequency electrosurgical knife is used throughout for the reason that it permits a more accurate dissection. Only three primary hemorrhoidal masses are removed. If secondary hemorrhoids are present, they are incised longitudinally and the veins carefully coagulated to conserve the mucosa.

The injection treatment of hemorrhoids has not been used by our group since 1937 because of a high recurrence rate associated with this method of treatment.

Fig. 6.

Fig. 7.

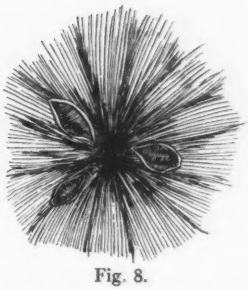

Fig. 8.

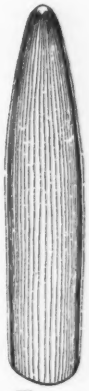

Fig. 9.

Fig. 6. By using the same chromic catgut suture the mucosa is closed. The dead space between the mucosa and the muscle is obliterated by passing 1 or 2 of the sutures through a small amount of muscle as the mucosa is closed. Closure extends to the pectinate line and the suture is tied.

Fig. 7. The skin at the base of the external hemorrhoid is incised with the electrosurgical knife with no traction being made on the mass. Once the skin has been incised, traction is made on the external hemorrhoid to expose more of the varicosities in order that these may be dissected out. Any bleeding points are clamped and ligated.

Fig. 8. The final appearance of the anal orifice after the completion of the operation. A simple vaseline gauze dressing is applied.

Fig. 9. Illustrating the shape of the dilator improvised from a paraffin candle. This is recommended for daily dilatation of the anal canal starting about 10 days after operation.

POSTOPERATIVE ORDERS

The usual postoperative orders are:

1. Give morphine sulfate 10 milligrams (1/6 gr.) every 4 hours *pro re nata* for 48 hours.
2. Ambulate the evening of operation.
3. Give liquid diet on day of operation; soft diet the following day.
4. Dress anus with vaseline gauze.
5. Give mineral oil enema, the morning after operation.
6. Give mineral oil emulsion with cascara 30 cubic centimeters each night.
7. Give hot sitz bath twice a day after 24 hrs.

POSTOPERATIVE CARE

On the fourth postoperative day the anal canal is dilated by gently inserting the gloved finger after which the patient is discharged from the hospital. He is given instructions to return to the rectal clinic in 1 week. On the patient's first return visit a digital rectal examination is performed and the patient is instructed to purchase a tallow candle and fashion it to a tapered point as shown in Figure 9. He is instructed to dilate his anal canal daily with this improvised dilator and to return weekly to the rectal clinic. He is requested to return to the rectal clinic for a digital rectal examination once a week until the anal canal has healed, usually a period of about 4 weeks. When the wounds have completely healed and when the anus admits the examining finger without difficulty, the patient is discharged.

PORPHYRIA

A Consideration in Surgical Diagnosis

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THE differential diagnosis of the "acute abdomen" is a problem with which surgeons are constantly faced and many well known conditions are regularly considered before diagnosis is established. There is, however, a little known disease, porphyria, that may present the clinical picture of an acute abdominal surgical condition. This disease has received relatively little attention in the medical literature and has escaped mention in the journals and textbooks of surgery because it has been considered to be rare. In the past 10 years it has been recognized with increasing frequency. For this reason, and also because surgical intervention, with rare exceptions, is contraindicated in porphyria, a brief summary is being presented in this paper.

Porphyria is a metabolic dysfunction of considerable physiological significance and it is considered to be due to an "inborn error" of porphyrin metabolism (5). The clinical picture is variable but is most commonly characterized by onset in early adulthood with symptoms of colicky abdominal pain, obstipation, and evidence of emotional and neurological disturbance in association with the excretion of dark or red urine.

CLINICAL DESCRIPTION

From the clinical standpoint the disease appears in three forms and may be classified in the following manner: (1) light-sensitive; (2) acute intermittent, or acute idiopathic; (3) mixed, with characteristics of 1 and 2. (Also called "chronic," a meaningless term, for porphyria is a chronic disorder with episodic recurrence.)

The clinical manifestations of porphyria, accompanied by the increased excretion of porphyrins in the urine and feces, are outlined in Table I. The light-sensitive type is rare and may infrequently be accompanied by a hemolytic anemia. The acute intermittent form is the most familiar guise of porphyria and may first come to attention following infection, exhaustion, trauma, during or after the puerperium, or with the use of barbiturates, sulfonamides, and alcohol. This so called "acute porphyria" often presents symptoms of abdominal pain and signs of intestinal obstruction at the onset of an acute attack, or it may closely simulate the syndromes of appendicitis, peritonitis, pancreatitis, perforated peptic ulcer (4), or cholecystitis. At other times, concurrence of hypertension, tachycardia, and nervousness in a patient may direct attention to a different anatomical site and lead to unnecessary thyroidectomy (13). The mixed form of porphyria is a clinical rarity and is less subtle in its clinical expression although it too may present abdominovisceral crises.

The natural history of porphyria has disclosed multiple appearances in families and suggests that the same metabolic fault is common to all three forms of the disease (3). The varying and often overlapping expressions of the disease appear to be related to the degree of sex maturity of the individual at the time of onset of attack. Usually, the light-sensitive type is observed in infancy and early childhood, the mixed form in adolescence, and the acute intermittent form after the period of adolescence. Aldrich cites 2 cases of the acute intermittent type in young children. The author has studied one individual who experienced episodes of abdominal pain, obstipation, and signs of intestinal obstruction at the age of 7; although dark urine was subsequently and intermittently present for more than two decades, no further symptoms attributable to porphyria were recorded over this period. Then a classical episode with marked neurological disturbance was precipitated by heavy

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Opinions expressed herein are those of the author and do not necessarily represent the view of the Bureau of Medicine and Surgery, Navy Department.

TABLE I.—CLASSIFICATION AND CHARACTERISTICS OF PORPHYRIA

Type	Onset	Sex distribution	Chemical findings in urine and feces	Clinical characteristics
Light-sensitive	Infancy or early childhood	M>F	1—Uroporphyrin I and coproporphyrin I. (Excreted continuously. Increased in erythrocytes and plasma)	1—Red urine
				2—Photosensitivity of exposed parts, scarring
			2—Porphobilinogen absent	3—Pigmentation of teeth, bones, and cartilages
			3—Fecal urobilinogen increased in presence of hemolytic anemia	4—Hirsutism
				5—Hemolytic anemia (rare)
Acute intermittent	Postadolescence (usually)	F>M	1—Uroporphyrin I in loose combination with a type III porphyrin (zinc complex), coproporphyrin III. (Smaller amounts of coproporphyrin I)	1—Dark, mahogany, or red urine; light urine turning dark on exposure to sunlight suggestive
			2—*Porphobilinogen positive*, intensely so during acute episodes; intermittently positive during latent phase	2—Nervousness, indigestion, and vague transitory pains
				3—*Personality disturbance* 4—*Visceral crises, obstipation*
				5—*Neuritis, myelitis,* and *paralysis*
				6—*Convulsive seizures*
				7—*Hypertension, paroxysmal*
				8—Tachycardia, hoarseness
				9—Pigmentation of the skin
				10—Normocytic anemia, resistant to treatment (occasional)
Mixed	Adolescence (variable)	M>F	1—Erratic production of porphyrins, qualitatively and quantitatively. (All of above types of porphyrins)	1—Dark, red urine
				2—Photosensitivity, moderate
			2—Porphobilinogen intermittently positive	3—Visceral crises
			3—Increase in protoporphyrin (rare)	4—Jaundice
				5—Paucity of central nervous system signs
				6—Pigmentation of skin moderate to marked
				7—Normocytic anemia, occasional

indulgence in alcohol. The role of this agent in directly increasing porphyrin excretion has been demonstrated (14).

Latent, asymptomatic porphyria has been observed in patients with other disease (miliary tuberculosis, kidney disease, fungus and bacterial infection) as a coincidental finding, and as a consequence of routine testing of the urine for porphobilinogen (2).

The vagaries of its clinical expression mark porphyria as "the simulator."

CASE SUMMARIES

The following brief case abstracts are illustrative of the clinical patterns of porphyria that are likely to be encountered by the surgeon. Since these cases were confused with appendicitis, cholecystitis, pancreatitis, intestinal obstruction and "tumor," they point out common diagnostic errors. An additional case abstract is presented to emphasize another facet of porphyria, its ability to cause paroxysmal hypertension.

Appendicitis and Complications

An 18 year old white female, a known case of epilepsy, complained of fever, nausea, and vomiting, lower right quadrant abdominal pain, obstipation, and severe headache for 10 days. She had long been regarded as suffering from "idiopathic epilepsy" and there were manifest mental aberrations. Physical examination disclosed generalized abdominal tenderness and distention. Laparotomy was performed for "appendicitis and complications." The patient died on the third postoperative day.

This patient (and other members of her family) passed red or dark urine intermittently, a fact that was not elicited. Onset of her last illness, with abdominal complaints predominating, was not correlated with her past medical history which gave a clear picture of the natural history of this disease. A finding of dark urine and the combination of convul-

sive seizures, obstipation, hysterical outbursts, and abdominal involvement point to something other than appendicitis.

Cholecystitis

A 20 year old white male was admitted for treatment of urticaria and, during routine examinations, a dark amber urine specimen was observed. The patient remarked that other members of his family also passed dark or red urine. Tests for porphobilinogen at this time were negative. A few days later an icteric tinge of the skin and sclerae was noticed. This became more intense and was followed by upper right quadrant abdominal pain, obstipation, nausea and vomiting. Distress continued unabated and the possibilities of the presence of both gall-bladder disease and intestinal obstruction were considered. Further observation disclosed inconstant areas of tenderness; hyperesthesia was not prominent. There was no leucocytosis. No stools were passed, nor were they recovered by enemas, for 8 days. Hepatocellular dysfunction as a cause of the jaundice was indicated by positive cephalin flocculation tests. In view of this evidence and the family history, medical management was continued with attention directed toward restoration of electrolyte balance. A positive porphobilinogen test, however, was not obtained for 3 weeks (3).

This patient is classified as a case of mixed porphyria (Table I), a form of the disease that is characterized by irregular excretion of porphobilinogen, abdominovisceral crises, and a paucity of neurological signs.

Acute Pancreatitis and Intestinal Obstruction

A 36 year old white male was admitted for repair of a hydrocele and was given barbiturates both for sedation and for anesthesia. Postoperatively, he complained bitterly of pain and expressed fear of death. Abdominal pain and distention appeared and obstipation was marked. Roentgenograms of the abdomen revealed several widely distended loops of intestine. Intubation did not relieve his distress and vomiting persisted. In view of the foregoing and the finding of an elevated serum amylase, intestinal obstruction in association with acute pancreatitis was considered. Laparotomy was performed but no abnormalities were observed. The patient became confused and unmanageable thereafter and a diagnosis of toxic psychosis was made. Phenobarbital was prescribed freely for sedation. He was transferred to a psychiatric ward and thereupon developed a flaccid quadriplegia. Recovery occurred after long hospitalization. He was discharged with a diagnosis of conversion hysteria. His difficulties returned a few months later following an attack of tonsillitis during which illness he received sulfadiazine and seconal. He eventually recovered after prolonged hospitalization and during this period clinical attention was directed to the color of his urine which provided the clew to a diagnosis of porphyria (9).

The "cardinal sign" of this disease was long present but a low index of suspicion of porphyria blocked earlier diagnosis. As a result this patient was subjected to needless surgery, dangerous sedation, and prolonged psychotherapy. This sequence of events is not an uncommon experience for the porphyric patient. A recent report described a case of acute intermittent porphyria that exhibited 4 abdominovisceral crises over a period of 27 years which led to 3 laparotomies because of the symptoms (10).

Tumor and Periodic Intestinal Obstruction

A 22 year old white female complained of pain in the lower right abdominal quadrant, weight loss, nervousness, and "anesthesia" for a period of 1 year. She was subject to frequent crying and fainting spells. Origin of the pain and the significance of an abdominal "tumor," intermittent in presence, were obscure. Roentgenogram of the abdomen disclosed many dilated intestinal loops. At laparotomy the tumor was found to be cecum filled with fecal material. The appendix (normal) was removed. The patient was discharged, unrelieved of her symptoms. Prior to operation, red urine was twice noted and the tests for porphobilinogen were positive.

The positive porphobilinogen tests rewarded a suspicion but the discovery of the "phantom tumor" diverted attention away from the obvious diagnosis. Again, the combination of emotional lability, abdominal pain and obstipation, and dark urine was prominent.

Paroxysmal Hypertension

A 40 year old housewife was hospitalized for symptoms persisting long after an epidemic of food poisoning in which she was a victim. Colicky abdominal pain and complaints of nervousness were recorded. A principal early finding was an extreme degree of hypertension, 240/140 millimeters of mercury, but that was subject to wide variation. A house officer's diligence in gathering a careful history added evidence of previous convulsive seizures, periodic vague illnesses, occasional dark urine, and an unexplained anemia. This led to investigation of the quality of the patient's urine specimens and early diagnosis.

This case illustrates a pattern of porphyria wherein hypertension is a significant finding; the resemblance of this case to the signs and symptoms produced by an adrenal medullary

tumor (pheochromocytoma) is striking. During an acute attack of porphyria there may be widespread evidence of vasospasm and this has been ascribed to a direct effect of coproporphyrin I on smooth muscle. Similarly, isolated loops of intestine (experimental animals) have undergone contraction when lavaged by dilute solutions of this same porphyrin (11). Indeed, much of the symptomatology of porphyria may be explained on this basis.

DIAGNOSIS

Examination of the urine excites suspicion of porphyria if the specimen is dark or if it darkens on standing, especially on exposure to sunlight. The urine specimens of patients suffering from acute intermittent porphyria often give a strong Ehrlich's reaction. The chromogen responsible for the reaction in these specimens is distinct from urobilinogen and is easily separable from it by the following test.

TEST FOR PORPHOBILINOGEN (WATSON-SCHWARTZ)

1. Equal parts of urine and Ehrlich's reagent (2 ml. of each) are mixed in a test tube.
2. To the foregoing mixture is added an equal volume of a saturated aqueous solution of sodium acetate.
3. Two milliliters of chloroform are added to the whole and mixed thoroughly by vigorous shaking.
4. A positive result is indicated by persistence of a pink-purple color in the aqueous fraction after centrifugation. (In doubtful reactions re-extraction of the aqueous fraction with chloroform is helpful.)

This simple test for porphobilinogen provides confirmation, since a positive result is considered pathognomonic of the disease. False positive tests are extremely rare (16). Porphobilinogen is regularly demonstrable in the urine of patients during an attack of acute intermittent porphyria. It is irregularly present in mixed porphyria and absent in pure light-sensitive porphyria.

In these latter instances uroporphyrin identification is necessary and this may be accomplished by means of chromatography, or by demonstration of characteristic absorption bands, melting points, and other physicochemical properties.

Excretion of uroporphyrin, by definition, is pathognomonic of porphyria and is usually accompanied by the excretion of coproporphyrin in increased amounts. Porphobilinogen is regarded as a colorless precursor of uroporphyrin.

BIOCHEMICAL BACKGROUND

The porphyrins are red pigments and are essential components of many living cells and of some bacteria. They are widely distributed in nature and play a fundamental role in metabolism. As the essential constituents of such substances as cytochrome, catalase, myoglobin, hemoglobin, and in the plant kingdom, chlorophyll, *they are intimately concerned with cellular respiration*. Any disturbance of porphyrin metabolism therefore is likely to be reflected in these substances.

The porphyrins have a basic structure of 4 pyrrole rings connected by methene bridges and contain 8 replaceable hydrogen atoms; if these 8 atoms are replaced by 4 methyl and 4 ethyl groups, 4 different combinations and 4 isomers are possible. They have been designated as types I, II, III, and IV. Only porphyrins corresponding with types I and III occur in nature and are of known clinical importance.

The appearance of uroporphyrin in the urine is considered pathological. A small amount of coproporphyrin is normally excreted daily in the urine and feces, 10 to 320 micrograms (14). Uroporphyrin received its name from its original source of isolation, the urine; coproporphyrin, from its source, the stool. Actually, uroporphyrin and coproporphyrin are found both in the urine and feces.

The coproporphyrins have 4 methyl and 4 propionyl groups; uroporphyrin differs in that its methyl groups have undergone carboxylation. Of considerable importance are the protoporphyrins, since heme is a product of the binding of iron to protoporphyrin. This group contains 4 methyl, 2 propionyl, and 2 vinyl groups at the substitution points.

Excellent reviews of the porphyrins are to be found in the reports of Watson and Larson (14) and Welcker (16).

TREATMENT

The management of episodes of acute intermittent porphyria is directed along protective

lines, i.e., the cautious use of chemotherapeutic agents and sedative drugs (especially the barbiturates), restoration of optimal electrolyte relationships, and avoidance of trauma, either physical or psychological. Demerol, 0.05 to 0.1 gram every 3 or 4 hours, is effective in control of pain; atropine is ineffectual.

Both liver extract and folic acid have been recommended but the efficacy of these agents has not yet been fully established. Calcium salts have been used with inconstant results in terms of ridding the body of excess porphyrins. Incomplete evidence that prostigmine is of benefit has been reported (6). The antihistamine agents have not been useful in this experience, but further trial is indicated.

Preventive measures during asymptomatic periods include general considerations of good hygiene in regard to diet and rest, avoidance of overexposure to sunlight, and prompt attention to all infections. The dangers inherent in self-medication, especially regarding the use of the barbiturates, and the calamitous results from alcohol imbibition, are to be emphasized.

In view of probable disorder in the cellular respiratory mechanisms in porphyria, the use of riboflavin, nicotinic acid and related substances (paba, etc.) would appear to be rational.

The light-sensitive form of porphyria may be accompanied by a hemolytic anemia and early reports indicate a sharp reduction in porphyrin excretion and loss of photosensitivity shortly after splenectomy (1).

When clear-cut indications for surgical intervention exist in a porphyric person, the foregoing precautionary measures should be kept in mind. The choice of anesthetic agent is important, for general anesthesia is undesirable. Local or block type of anesthesia is preferable.

DISCUSSION

Porphyria is not a rare disease and it occurs often enough to suggest its inclusion in the exercise of surgical differential diagnosis. In the Scandinavian and South American countries, especially Sweden (12) and Argentina (7), the syndrome is not unfamiliar to practitioners.

A review of protocols of over 100 cases of porphyria and personal observation of 16 additional patients have revealed that many of these individuals were subjected to one or more surgical procedures before porphyria was suspected. That these operations were probably unnecessary is shown by the fact that subsequent examination of excised tissue failed to detect pathological changes sufficient to explain the symptoms.

The disease has special significance for the surgeon since it may mimic any of the common abdominal emergencies. This creates a dangerous situation for the combination of preoperative sedation and trauma may cause progression of symptoms and a rapidly fatal termination.

Acute intermittent porphyria is the guise most commonly encountered and it provides the surgical pitfalls. Fortunately diagnosis may be established with rapidity in these particular cases by resort to a simple laboratory test for porphobilinogen.

CONCLUSIONS

1. Porphyria, especially the acute intermittent form, may first appear as "a surgical emergency."

2. Mimicry of intestinal obstruction, of gallbladder disease, of appendicitis, pancreatitis, perforated peptic ulcer, of pheochromocytoma, and even of hyperthyroidism has been observed.

3. Sedation and surgical intervention may exacerbate the fundamental disorder and lead to outspoken psychotic behavior with progressive and fatal neurological involvement.

4. The combination of emotional lability, abdominal pain, obstipation, and obscure neurological disturbance alone, or in association with dark urine, should excite suspicion.

5. Diagnosis is established (except in light-sensitive forms) by a positive test for porphobilinogen in the urine.

6. Adoption of the simple and reliable test for porphobilinogen is suggested as an added refinement of value in differential diagnosis.

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STUDIES ON BURNS

V. Experimental Study of the Effect of Heparinization and Gravity on Tissue Loss Resulting from Third Degree Burns

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THE amount of tissue loss following injury depends in part upon the state of the circulation in the injured area. In the case of damage by cold, Lange and others have demonstrated that heparinization lessens tissue loss by preventing vascular thrombosis. It has also been demonstrated that gravity effects the circulation of a region with decreased vascular supply and hence affects the amount of tissue loss (2). The dependent position results in maximum volume flow and decreased tissue loss. This study was undertaken to determine the effects of heparinization, elevation, and dependency, alone and in combination, on the amount of tissue loss after a standard thermal injury.

METHODS

White rabbits weighing 4 to 6 pounds, maintained on a standard laboratory diet, were used. Burns of the ear were effected by immersion in hot water after the method of Drinker and Glenn (3), with the animals under general anesthesia. Before burning, the hair was clipped as close as possible but not shaved. To determine the least degree of burn which would result in a reproducible area of slough, 26 ears were burned by immersion in water at various temperatures and for varying periods. It was found that immersion in water at 65 degrees C. for 5 seconds was the least degree of exposure which would repeatedly result in a large area of slough. This was accepted as the standard burn.

The animals were heparinized by administering 5 milligrams of heparin intravenously and 10 milligrams subcutaneously immediately after burning and then 10 milligrams subcutaneously every 4 hours for 7 days. This dosage maintains the coagulation time above 12 minutes as compared to a control of 2 to 3 minutes as checked in many animals in this and other studies in this laboratory.

In the elevation experiments the ears were maintained in an elevated position for 7 days by means of a loosely fitting wire cage. The brace did not interfere with the animals' activity nor result in pressure about the neck or base of the ears.

Circulatory changes in the burned area were studied by means of the fluorescin test. Fluorescin in a dose of 0.75 cubic centimeter was injected intravenously and the burned areas observed under a long-wave ultraviolet lamp equipped with a Wood's filter. Observations were made ½, 4, 24, 72, 96 and 124 hours after burning.

The total area of tissue loss was determined in 9 animals in each group by planimeter measurements on tracings of the ears before burning and after tissue sloughing was complete.

The standard burn was carried out on 85 ears. Each ear was burned from the tip up to a tattoo mark three-fourths of the way to the base. The animals were divided into four groups (Table I).

Group I, control (26 animals), received no treatment.

Group II (26 animals) received heparin for 7 days with ears dependent.

Group III (18 animals) received no heparin, but the ears were kept elevated for a period of 7 days.

Group IV (15 animals) received heparin for 7 days and the ears were kept elevated for the same period.

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RESULTS

In Group I, the control animals which did not receive heparin and whose ears were allowed to remain dependent, massive edema developed rapidly and persisted for 8 to 10 days. There was an average tissue loss of 52.4 per cent of the burned area.

In Group II, in which the animals were heparinized and the ears were allowed to be dependent, edema appeared rapidly, but it was never greater than and often less than the amount accumulating in the other three groups. The edema in this group also was present for 8 to 10 days. Gangrene did not appear until 4 to 5 days after burning. Tissue loss in this group was less than that occurring in any of the other three groups, averaging 40.7 per cent of the burned area.

In Group III, in which the animals were not given heparin and the ears were kept elevated, there was rapid development of massive edema. This was grossly equal to the edema in Group I animals, but the swelling decreased rapidly, disappearing by the sixth day after burning. Gangrene developed rapidly in this group, appearing within 48 hours. The average tissue loss in this group was 63.1 per cent of the burned area.

In Group IV, in which the animals were heparinized and the ears kept elevated, there was rapid development of massive edema, but as in the group in which no heparin was given and the ears were kept elevated the edema disappeared rapidly, not being evident by the sixth day. Gangrene developed in 72 to 96 hours. The average tissue loss in this group was 65 per cent of the burned area.

The fluorescin test demonstrated the presence of excellent circulation in the burned area in all animals during the first 4 hours after burning. Twenty-four hours after burning there was absence of fluorescence or only mottling in the burned area in all animals which did not receive heparin. Gangrene ultimately developed if at 24 hours after burning fluorescence was absent or only mottling occurred. Fluorescence persisted for varying lengths of time in the animals which received heparin. Two of these showed diffuse fluorescence in the burned area through the fifth day and did not develop gangrene.

TABLE I.—EFFECT OF DEPENDENCY AND ELEVATION, WITH AND WITHOUT HEPARINIZATION

	Edema		Onset gangrene hours	Tissue loss per cent
	Degree	Duration days		
Group I (dependent)	++++	8–10	60–72	52.4
Group II (dependent, heparin)	+++	8–10	120	40.7
Group III (elevated)	++++	5–6	48	63.1
Group IV (elevated, heparin)	++++	5–6	72–96	65.0

DISCUSSION

In this series of experiments the studies made with the fluorescin test show that during the first few hours after the burn there was excellent circulation throughout the burned area. This was true even though the burn was severe enough to result eventually in sloughing of the tissue. This excellent circulation continued for at least 4 hours after the thermal injury. By the twenty-fourth hour, vascular occlusion was demonstrated and dry gangrene subsequently appeared in these areas. Because of the delay in the development of vascular occlusion, it was hoped that thrombosis could be prevented if heparinization was started within 4 hours after the injury. If this resulted in the preservation of an adequate circulation, then it might be possible to maintain the viability of injured epithelial elements that would otherwise die as the result of poor blood supply. It would not of course, be possible to benefit in any way tissue that had been coagulated.

It was demonstrated that heparinization alone resulted in less tissue loss than occurred in the control animals. Also, gangrene did not appear until about 2 days after it had done so in the control animals. If the ears were elevated, however, regardless of whether or not the animals were heparinized, dry gangrene appeared sooner and the tissue loss was definitely greater than in the control animals. Of the two groups of animals with ears elevated, gangrene appeared about 2 days later in the heparinized animals.

The edema fluid was as massive in the ears that were elevated as it was in the dependent

ones; however, the edema disappeared much more rapidly in the former.

Landis showed experimentally that the capillary pressure of a limb varies inversely with the height of the capillary above the heart. In the same series of experiments he also demonstrated that there was a markedly increased capillary pressure following injury, especially if the trauma was due to heat. It is probable that the great capillary dilatation and increased capillary pressure that occurs during the few hours after burning is at first sufficiently great to overcome the effect of elevation in decreasing the capillary pressure. This would explain the massive edema that occurred in the ears in spite of elevation, especially since it is known that most of the edema of burns accumulates within the first few hours after injury. Somewhat later the decreased capillary pressure due to elevation apparently becomes relatively more effective. This not only decreases the venous capillary pressure and improves the venous outflow but also decreases the arterial capillary pressure and thus diminishes the blood supply to the part. This resulted in the earlier appearance of dry gangrene and more extensive tissue loss in the elevated ears than in the dependent ears.

This study was carried out on third degree burns of relatively small areas. Its results are not to be applied clinically as it has been previously demonstrated that the use of heparin definitely increased the mortality of burns (1).

CONCLUSIONS

The results of the present experiment on the burned rabbit's ear seem to justify the following conclusions:

1. There is a delay of at least 4 hours after thermal injury before vascular occlusion occurs, provided the burn is not severe enough to cause immediate complete coagulation of the epithelium.

2. Heparinization apparently delays the onset of dry gangrene and diminishes the amount of tissue loss.

3. Although elevation increases the rapidity of disappearance of edema fluid, it does not appreciably diminish the degree of immediate accumulation.

4. Elevation as compared with dependency is associated with the more rapid appearance of dry gangrene and an increase in the amount of tissue loss. Apparently, therefore, it overbalances the beneficial effect of heparinization.

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THE FACTORS INVOLVED IN THE MANAGEMENT OF THE SURGICAL COMPLICATIONS OF POLYCYSTIC DISEASE OF THE KIDNEY

A Report of 21 Cases

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THE purpose of this discussion is to consider the factors which are responsible for polycystic kidney disease, and which should govern the surgeon in the management of the complications arising in this disease.

Whether the case is one of a large kidney from the increase in the size of the cysts, hematuria, infections with threatened sepsis, or stone formation which interferes with the urine drainage, the treatment should be on a conservative basis, with the thought of preserving the kidney, even though there is only a minimum degree of kidney function when the complication is recognized.

This study was prompted by 2 cases of polycystic kidney disease in which, some years previously, nephrectomies had been performed. In 1 case, that of a 46 year old woman, one kidney had been removed 3 years before, and the other was now involved. The pathological report showed that in the removed kidney only 8 per cent of the counted glomeruli were found to be hyalinized. The patient expired 10 days after hospitalization from renal failure, with terminal uremia. In the other case, that of a 41 year old woman, one kidney had been removed 4 years previously, and the pathological finding was that only 7 per cent of the counted glomeruli were hyalinized. The patient died 2 weeks after entering the hospital from failure of the remaining kidney, with terminal uremia.

The large proportion of functioning glomeruli found in the resected kidneys in these 2 cases suggested that if, instead of being removed, they had been dealt with surgically in a conservative manner, the patients' lives might have been prolonged. In each case, the removal of one kidney threw a heavier burden on the remaining kidney and hastened renal failure.

The disease is found in the newborn and in adult life. In infants, death may occur in utero, and on account of the enlarged kidney, normal delivery in many instances is interrupted by fetal dystocia. The majority of infants with the disease die upon cessation of fetal circulation. Babies that survive this stage usually live only a short time before dying from renal failure. In the occasional case of an infant surviving for a few years, evidence of renal rickets or renal dwarfism will appear, with characteristic bone changes simulating hyperparathyroidism and pituitary disturbances, as noted by Kretschmer.

In the adult, polycystic kidney disease is more of a graded involvement of the renal tissue, and is usually recognized from the third to the sixth decade of life. In cases presenting a minor degree of renal involvement, patients may live their normal span of life only to show slight renal damage in later years. The cases of Grade II and Grade III, with 50 to 75 per cent of the uriniferous tubules potentially cystic, are usually the ones in which surgical complications occur.[1]

This study of 21 cases of polycystic disease of the kidney is taken from the files of the two Baptist Hospitals and the Jefferson-Hillman Hospital in Birmingham, Alabama, covering a 10 year period, from January 1, 1939, to January 1, 1949. Two of the cases were of infants and 19 were of adults. Death occurred

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[1]The degrees of renal involvement: In Grade I, up to 25 per cent of the glomeruli are involved; in Grade II, from 26 to 50 per cent; in Grade III, from 51 to 75 per cent, and in Grade IV, from 76 to 100 per cent.

in the case of one infant at birth and the other at 3 months of age. Both had bilateral polycystic disease of the kidney and died from renal failure.

In the adult cases, the disease was recognized in the fourth to the seventh decade of life, and all 19 presented complications in one form or another. In 1 case, that of an 83 year old man, a polycystic condition was present, but owing to advanced cardiovascular renal disease which proved fatal a few days after hospitalization, it was not recognized until an autopsy was performed.

In the adult group there were 9 females and 10 males. The youngest was 35 years old, and the oldest was 83. The average age was 50. The chief complaints or symptoms were: hematuria in 2 cases; urinary complaints in the form of frequency, dysuria, and the like in 9 cases, and in 11 cases there was pain in the kidney or flank region with varying degrees of kidney enlargement to where the kidney size was readily recognized by bimanual palpation. (Some patients, of course, showed more than one of these symptoms.) In 6 cases the symptoms were largely medical, in line for renal failure associated with cardiovascular changes, and polycystic disease was recognized by clinical study, retrograde pyelogram, or at autopsy. In 2 cases the diagnosis was made at autopsy. In one of these, death resulted from general peritonitis caused by perforation of the sigmoid colon following unrecognized strangulated inguinal hernia. In the other case the patient had extensive second and third degree burns of the body surface to which he succumbed in a short time. Evidently polycystic disease of the kidney did not bring about either of these deaths.

In 16 of the cases bilateral polycystic kidney was present. Of the remaining 3 cases in which unilateral polycystic kidney was considered to be present, 1 patient died of renal failure. Autopsy revealed the left kidney to be enlarged (570 grams). The right kidney was clear of cysts but atrophic. In the 2 remaining cases of unilateral polycystic kidney nephrectomies were performed with removal of enlarged and infected kidney. One patient who had a left nephrectomy 10 years ago has been examined recently, and no apparent enlargement of the kidney was found, but the patient has a definite renal damage with acidosis, nonprotein nitrogen 74 milligrams, creatinine 5.4 milligrams, with albumin, casts, pus, and blood in the urine. The other patient has not reported for treatment since his operation in 1945.

Ten cases were handled medically and 7 surgically—5 nephrectomies and 2 nephrostomies. The remaining 2 cases were not dealt with for polycystic kidney disease, but for other conditions, which have already been described. Results from the 5 nephrectomies were: 3 of the patients died within 5 years after the kidney was removed, and the other 2, when they last reported, presented a picture of renal failure. The chief complaint these 5 patients offered before operation was enlargement of the kidney with graded infection. Pathological reports on 2 of the resected kidneys revealed a good amount of normal renal tissue. In 1 case, only 8 per cent of the counted glomeruli were hyalinized, and in the other only 7 per cent.

ETIOLOGY AND PATHOGENESIS

Polycystic disease of the kidney is the result of an embryonal defect, with formation of cysts, principally in the secretory portion, and to a less extent, cysts and aplasia of the collecting tubular portion of the kidney. This impairs union of the secretory and collecting tubules, and interferes with drainage.

The disease is bilateral or potentially bilateral in all cases. This fact heightens the importance of conservative treatment when one kidney is involved, because it is apparent that if a nephrectomy is performed, cyst formation in the remaining kidney will be hastened.

Heredity is one of the most important factors in the etiology of the disease. Of the 2 cases in the series under discussion in which the family history was traced, polycystic disease of the kidney was found as far back as the third generation in one instance, and the second generation in the other.

The tendency to the anomaly may be transmitted by either sex, and apparently it is carried by a dominant gene. It is not known whether persons without symptoms, who transmit the disease to their offspring, have

normal kidneys or a subclinical or potential form of cystic kidneys, according to Bell.

Spemann and other embryologists have found through experiments on the lower vertebrates that differentiation of the embryonal cell is normally dependent upon the following factors: (1) the intrinsic predisposition within the primitive cell to undergo specialization, or cell competence, and (2) an inductor or stimulant of a chemical nature elaborated by certain previously specialized cells, commonly called organizers.

For the normal development of the different body organs, there must be a harmonious interplay of cell competence and organization. Lack of this harmonious interplay causes malformations in the development of body organs, such as polycystic kidney and its associated anomalies, and many others. The organizer concept is now generally accepted by embryologists and anatomists as the explanation of such malformations.

The nature of organizers is explained simply, briefly and clearly by Arey (1):

"It can be demonstrated during development that various localized parts of an embryo, called organizers, exert definite, directive influences on neighboring parts. Two kinds of effects are produced, and true organizer material exhibits both. The first is a simple activation by one region that arouses or releases inherent developmental potentialities in an appropriate reacting field. Such 'induction' is due to some general, unspecific property of tissues, living or dead. This is shown by the capacity of the activating principle (apparently chemical; perhaps involving glycolysis) to survive such treatment as boiling or alcoholic fixation. But there is more to organizer action than the mere eliciting of activity in a field, without displaying any itself. A true organizer is also able to impose organization upon regions that come under its influence. That is, it instructs the region in a kind of differentiation that it otherwise would be incapable of displaying.

"Two illustrations will perhaps make these matters clearer. If an ear vesicle of a frog embryo is transplanted under the flank it induces the formation of an extra limb there; but transplanted dead matter can accomplish the same result. On the other hand, an optic vesicle transplanted into an indifferent region, such as the belly skin, calls forth the differentiation of a lens in the overlying ectoderm (epidermis), just as occurs normally in the appropriate region of the ectoderm of the head."

In Figures 1 to 6, stages of embryonal development are illustrated, with accompanying explanations. Figures 7 and 8 illustrate the 3 stages of kidney formation.

Older theories of the cause of polycystic kidney disease, now chiefly of historical interest, included Virchow's hypothesis of a fetal inflammation resulting in connective tissue formation which obstructed the urinary channels, producing retention cysts. Another was the view held by Ribbert and others that the disease was the result of a defective union between the secretory and collecting tubular portions of the kidney. Herxheimer advanced the theory that polycystic kidney was a form of hamartoma, a tumor-like nodule of superfluous tissue, including embryonic mesenchyme, muscle tissue deposits, and lymphocytes.

More recently (1923) Kampmeier expressed the belief that polycystic kidney resulted from aplasia of the ureteric system. According to his theory, when the ureteral bud meets the renal blastema, it divides, and each new bud thus formed becomes covered by a cap of metanephronic tissue which normally would differentiate into a tubule, but pathologically may become detached and persist as a cyst. A still more recent writer on the subject, Lambert, says that this theory could explain the formation of cysts in the central portion of the kidney corresponding to the first dichotomous divisions of the ureter, but not the widely scattered cysts of polycystic disease.

Moolten says that the appearance of cellular hyperplasia caused many of the older authors to think that polycystic disease is a form of benign neoplasm (cystadenofibroma). He points out, however, that hyperplasia in the sense of excessive cellular proliferation is not characteristic of the lesion, either in the kidney or in the liver. He continues:

"The papillary projections within the greatly dilated perilobular ducts and convoluted tubules are best regarded as aspects of an imperfectly controlled growth of tissues, which is a process more akin to gigantism than to hyperplasia. The organizer concept makes it possible to explain both the immaturity and the gigantism of these elements on a single basis. If it is assumed that at a crucial stage of ontogenesis failure or inhibition of organizer activity occurs within certain tissues (periportal and nephrogenic mesenchyme), a corresponding failure or inhibition of differentiation may be expected. As this stage is succeeded by another, in which new

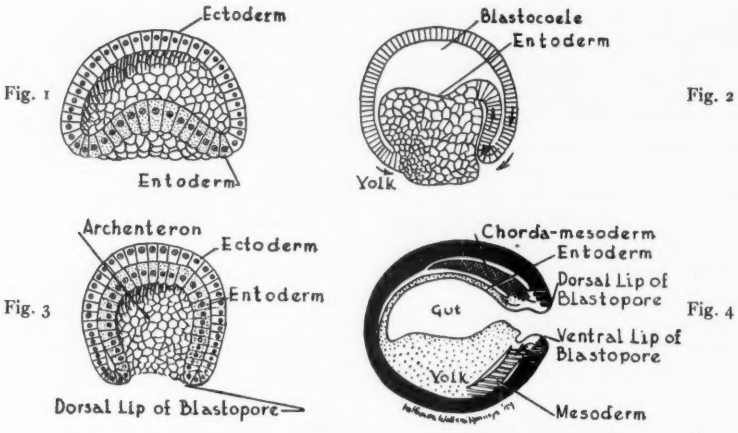

Fig. 1. The amphibian blastula, showing the beginning of invagination, or rolling in, of surface cells to form the blastopore.

Fig. 2. The characteristic horseshoe shape of the blastopore is beginning to form, as the entoderm rolls in under the ectoderm.

Fig. 3. Completion of invagination finds the entoderm underlying the ectoderm from one point of the horseshoe to the other, enclosing the archenteron, with the points forming the lips of the blastopore.

Fig. 4. The blastopore, showing the dorsal and ventral lips. From the dorsal lip are derived the cells, commonly called organizers, which perform the task of cell organization. This is called the chorda-mesoderm field. From the ventral lip mesoderm cells are proliferated. The dorsal lip of the blastopore in lower vertebrates corresponds to the primitive streak in the human embryo as the source of organizer cells.

organizers supersede previous ones, further differentiation passes these tissues by and they remain 'stranded . . . in a condition of permanent embryonicity.' The intrinsic growth energy within the cells of the affected tissues is not diminished, however, and as a result they continue to grow. Because of their loss of competence their growth is imperfectly controlled by organizers which normally govern differentiation and as a consequence they may continue growing until they reach an enormous size."

The clinical picture of polycystic kidney disease, as seen in adults, shows graded nephritis appearing about the third or fourth decade of life in most instances, usually with lumbar pains and an increase in serum nonprotein nitrogen. There may often be hematuria from ruptured cysts, and cardiovascular changes, such as sclerosis, hypertension and changes in the size of the heart. Albuminuria is a late finding. Most important in diagnosis of the disease is careful bimanual examination for kidney enlargement, and retrograde pyelogram for changes in the shape of the kidney pelvis (staghorn deformity).

Structurally, the thing of importance in polycystic kidney of the newborn is that the cystic nephrons are closed systems and do not communicate with the pelvis.

Anatomically, in both the newborn and the adult, the cysts develop as glomerular, tubular, or excretory cysts. Often in cases of glomerular cysts the glomeruli are found closed, usually leading to cul-de-sac pouch, but not to a patent convoluted tubule. In both the newborn and the adult, glomerular cysts appear as closed systems. In most cases in the newborn, the nephron itself is closed, which explains why they live only a short time. In adults, cysts occurring in the tubular portion of the uriniferous tubules are as a rule connected with the collecting tubules and the renal pelvis, which explains why the disease is slower in manifesting itself.

Polycystic tubules in the adult are still capable of filtration and concentration, as laboratory experiments recently have shown by injection of inulin and other substances (11).

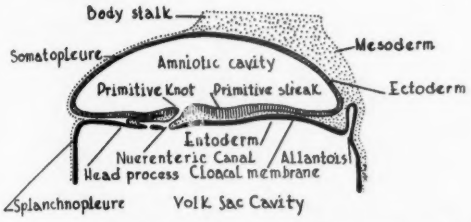

Fig. 5. Schematic median longitudinal section of a human embryo, at the stage of the head process and neurenteric canal (after Scammon). The beginning of the period of the embryo, at the end of the second week of pregnancy, is marked by the formation of the embryonic plate or disc, which soon consists of the three primary germ layers. This results from a flattening process in the embryonic region, by means of which the floor of the early amnion sac (ectoderm) and the roof of the yolk sac (entoderm) are brought into apposition. The embryonic disc, an oval plate, forms the embryo. Along the upper surface of the embryonic disc the primitive streak is formed. Simultaneously, by proliferation and migration, mesodermal cells spread out from the ventral surface of the primitive streak between the ectoderm and the entoderm. The portion of the primitive streak which produces the notochord, or head process, is the primitive knot, or Henson's node. The primitive streak in the human embryo is analogous to the dorsal lip of the blastopore in lower vertebrates as a source of mesodermal organizer cells possessing many and varied potentialities. From the primitive streak are derived the fundamental germ layers which develop into the various tissues and organs of the body, as Arey explains (2).

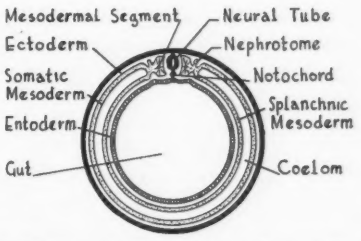

Fig. 6. Transverse section of the embryo at the end of gastrulation. The cellular districts have taken on the definite character of their prospective development. The various subfields which have formed—e.g., the notochord, bilateral somites and nephrotome—now take charge of development each within its own domain. The result is the formation of the notochord, myotomes, pronephrons, neural tube, somatic (outer) mesoderm, splanchnic (inner) mesoderm, and the celom. From the celom, which is formed by the separation of the outer and inner mesoderm layers, are derived the pleural sac, pericardial sac, and the peritoneal cavity. The gastrointestinal tract is derived from the splanchnic mesoderm and the body wall from the somatic mesoderm. The kidney is a mesodermal structure. It first appears as the nephrotome bud, located on each side of the notochord. It lies between the seventh and the fourteenth somites, medially, and between the notochord and the celom laterally.

MANAGEMENT

Polycystic disease of the kidney is primarily a medical problem. Surgery is indicated only when complications arise that are not amenable to a well organized medical treatment.

The disease is usually slow in development in the adult, and much can be done medically to prolong the lives of patients and make them comfortable. Such patients should be advised concerning the dangers of all infections that may lead to a destruction of renal tissue from the formation of sclerosis or scar tissue in the renal parenchyma. Their social activities should be temperate. They should have rest, both mental and physical. Cold and damp weather should be avoided. The diet should be of a low protein type.

The surgical complications seen in polycystic disease of the kidney are in great measure the result of graded infections and sclerosis, which interfere with drainage, and stone formation. Among the complications are: infection of the kidney tissue proper and the perirenal bed; hemorrhage (hematuria); intractable pain from the increasing distention within the cysts and infection which does not respond to medical measures; calculus or stone formation, either in the pelvis or the calyx of the kidney or ureter, and destruction of renal tissue from the pressure of the renal cysts.

Infection of the kidney which fails to respond to present-day antibiotics (penicillin, aureomycin, and the like) demands surgical drainage to save the kidney tissue, and to prevent general sepsis. This is accomplished by nephrostomy, which evacuates the larger cysts and drains both the kidney and the perirenal space. Lowsley and Curtis have suggested that if the kidney is found functionally dead prior to surgery, nephrectomy should be done. Contrary to this view, our experience has shown that the infection inhibits renal function, and that after the tension within the kidney has been relieved by surgical drainage, there will be sufficient renal tissue present to enable the kidney to do graded work. The renal tissue cannot be properly evaluated during the period of infection.

Hematuria is caused by rupture of the inflamed cysts into the calyx or pelvis of the

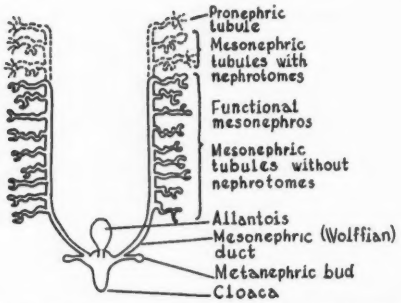

Fig. 7. Formation of the two transitory kidneys and the permanent or true kidney. Shortly after the nephrotome bud appears (Fig. 6), it develops into a series of tubules. This is the first or head kidney, or the pronephros. It appears about midway of the third week of pregnancy and is short-lived, usually functioning for approximately 10 days. The second kidney, or the mesonephros, is more developed, more differentiated and longer-lived (4 to 6 weeks) than the pronephros. The mesonephric tubules are derived from the intermediate mesoderm the same as the pronephros. From the mesonephros is formed the wolffian body, also transitory, which is the site of the future renal blastema. The wolffian body reaches its maximum size at the end of the second month of pregnancy, when it extends from the lung anlage above to the lower end of the gut tube, or cloaca, below. At this time it begins to regress, and regression contines through the fourth month of fetal life. When it has gradually atrophied, it is replaced by the newly formed third or true kidney, or the metanephros, as the excretory organ. Part of the wolffian body persists for a longer time and helps to form a portion of the sex glands. The metanephros has a dual origin. Its ureter or collecting portion arises from the lower end of the wolffian duct before it enters the cloaca. The secretory portion of the kidney is the renal blastema. As the ureter bud develops from the lower end of the wolffian duct, it grows rapidly in a cephalic direction, collecting about its dome portion the renal blastema tissue for the formation of the true kidney (13, 14).

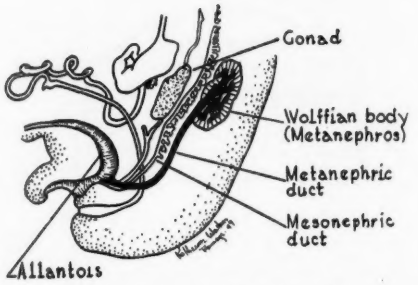

Fig. 8. The true kidney. As the metanephric or ureter bud grows from the lower end of the wolffian duct (Fig. 7), differentiation occurs. The pelvic end of the ureter diverticulum expands within the investing mass of renal blastema to form the major calyces, which subdivide into the minor calyces. This process results in the formation of numerous sprouts which become collecting tubules. The secretory or uriniferous tubular portion of the true kidney is made up chiefly of mesodermal cells arranged in small vesicular masses adjacent to the blind end of the collecting tubules. These develop into uriniferous tubules, which consist of a glomerulus, two limbs known as the descending and ascending limbs of Henle, connected by the loop of Henle, and two convoluted portions of the tubule. For fuller explanation the reader is referred to Patten and Piersol.

kidney. The treatment of hematuria is both medical and surgical. In recent years, rutin, a flavone or glucoside of green buckwheat, containing both vitamins C and P, has been employed with good results in controlling bleeding of polycystic kidney. It is given in dosage of 20 to 40 milligrams 3 times a day. Foucar reported dramatic results from the use of rutin in a case of hemorrhage of polycystic kidney.

The surgical treatment for hematuria that fails to respond to medical measures consists of opening the cysts down to the pelvis, but not into the pelvis, and drainage of the kidney.

Urinary calculus in the kidney or ureter complicating polycystic disease, resulting in the blockage of urinary flow, which invites infection, should be removed by nephrolithotomy or ureterolithotomy instead of repeated cystoscopic or ureteral manipulations.

For the progressive enlargement of the kidney accompanied by dull, aching pain in the lumbar region that is not relieved by medical measures, exploration of the kidney surgically is indicated. Exploration and biopsy will establish the diagnosis between neoplasm of the kidney and polycystic disease when clinical investigation, such as retrograde pyelogram, has failed. In the differentiation of the two conditions, polycystic kidney is easily recognized by finding elevated purplish cystic masses along the cortical surface as well as the medullary portions of the kidney.

Nephrectomy is the choice of procedure if neoplasm is found, whereas in polycystic disease, nephrostomy should be done, rupturing the larger cysts, with free drainage.

Rovsing in 1910 advocated drainage of the larger cysts by puncturing with free incision, and this procedure has carried his name since then.

Goldstein in 1935 recommended, in addition to Rovsing's rupture and drainage principles,

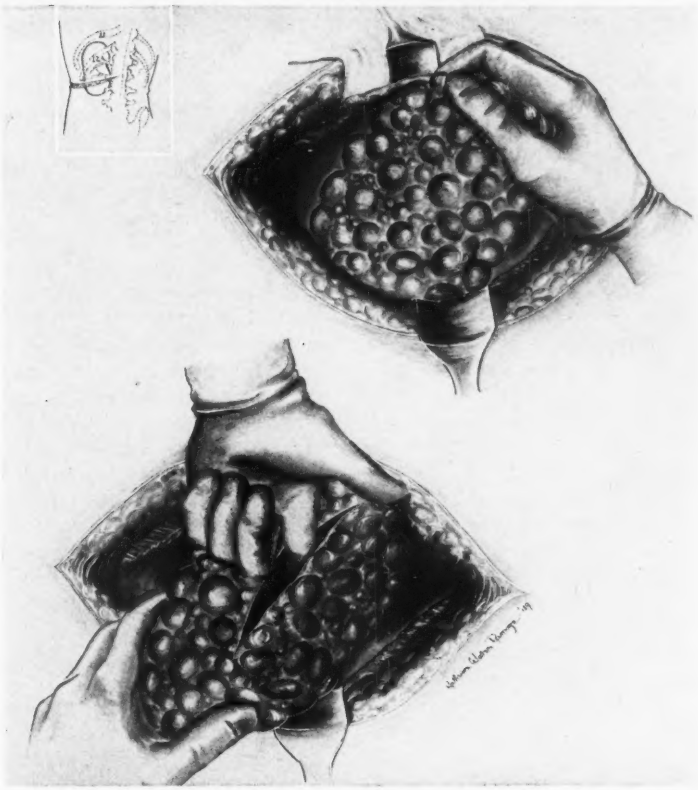

Fig. 9. Top, Kidney has been delivered into the wound through a transverse abdominal and lumbar incision preparatory to opening and drainage of cysts. Bottom, Showing line of the incision into the kidney placed posterior to the midportion, and finger in opening for rupturing the larger cysts.

decapsulation and excision of the cysts, nephrostomy up to but not into the calyces, nephropexy and establishment of nephrocutaneous (nonurinary) fistulous tract. Subsequently, if the cysts re-formed, they could be punctured without major surgery, since the kidney would be anchored adjacent to the subcutaneous tissue, he contended. Objection has been offered to Goldstein's operation on the ground that fixation of the kidney near the skin surface tissue may invite infection of the kidney that could lead to nephrectomy.

More recently, Young has advocated the destruction of the cyst by puncturing and replacement of the cyst fluid with a sclerosing material (5 per cent sodium morrhuate) in proportions of 1 cubic centimeter of sclerosing fluid for every 10 cubic centimeters of cyst fluid withdrawn.

Koehler cites the use of "varicocide," a proprietary preparation, as a sclerosing fluid. Instead of injecting the sclerosing fluid into the cysts, the cysts are opened and the outer walls excised, and the sclerosing preparation is applied to the cavity.

"Very fine surgical judgment is needed," Lowsley and Curtis point out, "in deciding whether or not to intervene surgically in cases of polycystic kidneys with relatively normal function but showing evidence of rapid progression of renal destruction despite suitable medical regimen. If such progression is occur-

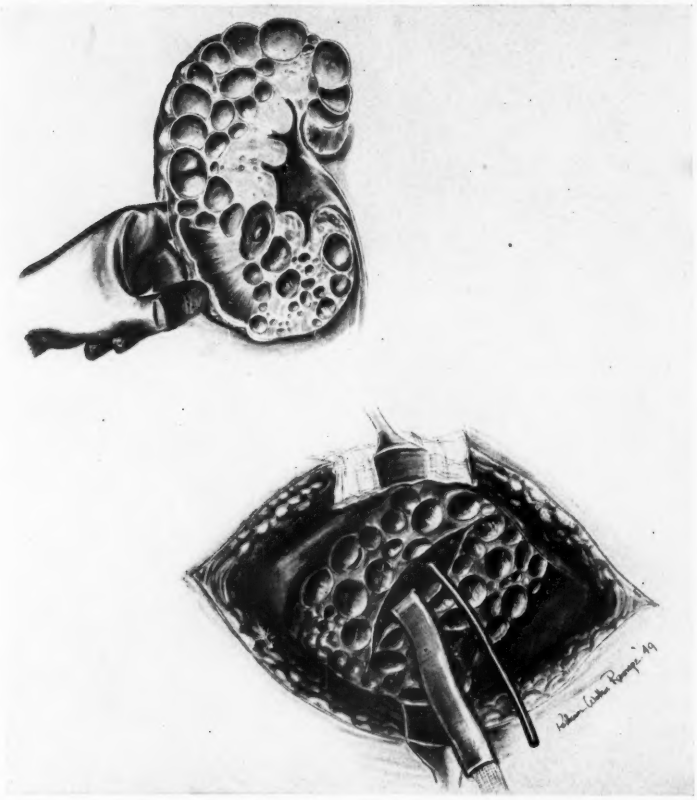

Fig. 10. Top, Hemisection of kidney with finger rupturing cysts, resulting in reduction in size of kidney. Bottom, Larger cysts having been opened, cigarette drains are left in kidney, usually for 8 to 10 days, depending on degree of infection.

ring at a rapid rate in the absence of infection or calculous disease, incision and drainage of the cysts (Rovsing's operation) may do much to prolong the patient's life. If periodic checkups reveal that renal destruction is progressing slowly, over a long period, this procedure, in our opinion, is not justified."

OPERATIVE PROCEDURE

Spinal anesthesia should be used unless it is contraindicated, because it gives the best relaxation of the tissues for good kidney exposure.

The transverse abdominal and lumbar incision is preferred to the oblique lumbar approach. It minimizes the danger of hernia and injury to the nerve supply (chiefly the iliohypogastric and ilioinguinal nerves, which are frequently injured in the oblique lumbar incision). The transverse incision will also increase the operative field exposure. The incision should be of such distance below the costal or rib border (4 to 6 cms.) that the suture line will not encroach on the cartilage or rib tissue. After incision of the aponeurosis fibers of the external oblique muscle, the internal oblique and transversus abdominis muscle fibers are split in line of their course. On reaching the perirenal space, the peritoneum is reflected medially, thus minimizing chances for injury to the peritoneum. The Gerota fascia is incised in line with the transversalis

fascia fibers, giving a free exposure of the kidney.

To minimize bleeding, the incision through the capsule and cortical portion of the kidney should be a longitudinal one placed slightly posterior to the center line of the kidney, known as Broedel's line. In this area the larger anterior kidney vessels will not be encountered, and thus troublesome bleeding may be avoided. The cysts are found chiefly in the cortical and to a less degree in the medullary portions of the kidney. They should be collapsed by puncture and excision of the roof of the cysts. Employment of an escharotic to the open cyst sacs is an individual thought. It may have some value in destroying the lining of the cysts. But the maximum result is obtained by thorough collapsing and excision of the larger cysts and drainage of the kidney and the perirenal space by use of cigarette drains. The incision in the kidney should be loosely approximated with interrupted chromic surgical suture about the Penrose drains, with free drainage of the perirenal bed.

Fig. 11. Photograph of divided left kidney removed at autopsy from woman patient, 46 years old. Her other kidney had been removed about 3 years before for polycystic disease. Specimen shows cysts of varied sizes. There was almost complete destruction of the kidney. Pathological examination revealed only a small amount of renal parenchyma remaining. Patient died of renal failure with terminal acidosis and uremia.

SUMMARY AND CONCLUSIONS

1. The treatment of polycystic kidney disease should be on a conservative basis. The disease is bilateral or potentially bilateral, and sacrificing a diseased kidney will result in an insult to the other kidney, which may lead to a similar condition.

2. The disease is found in the newborn and in adult life. Infants with the disease usually die at birth (sometimes in utero) or within a short time after birth. In adults, the disease usually manifests itself in the third to the sixth decade of life. The pathological changes and anatomical differences in the cysts of the newborn and the adult explain why the former usually die at birth or soon after, while in the latter the disease is usually not recognized until middle life.

3. A series of 21 cases is reported, and evidence is offered to show that a good amount of normal renal tissue may be present in a polycystic kidney. The renal tissue cannot be properly evaluated during infection.

4. Polycystic kidneys and other congenital malformations are caused by embryonal cell defects, which result from failure or inhibition of cell differentiation and organization.

5. The treatment of the disease is a medical problem unless complications arise that are not amenable to medical treatment. When surgery is necessary, its approach should be directed toward relieving the complication and preserving the kidney, except where neoplasm is found, when nephrectomy should be done. When an enlarged kidney presents doubt as between polycystic disease and malignancy, differentiation should be established by exploration and biopsy.

6. The transverse abdominal and lumbar incision is preferred to the oblique lumbar incision, because it minimizes the danger of nerve injury and hernia, and gives better exposure of the kidney.

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FRACTURES OF TARSAL AND METATARSAL BONES

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THE purpose of this paper is not to elaborate techniques for the treatment of individual fractures in the tarsus and metatarsus. Its purpose is rather to emphasize the general principles which should be kept constantly in mind when the injured foot is treated. Because of the fact that fractures of the os calcis have received so much consideration in the literature, they will not be specifically considered in this paper. However, the surgical principles to be outlined are also pertinent to a rational approach to the treatment of fracture of the os calcis.

In the treatment of fractures of the bone of the foot, it is paramount to keep in mind certain facts concerning (1) the function of the foot and (2) the pathology of trauma.

The foot, with the toes, is made up of 26 bones of varying shape and size. These bones are bound together by ligaments to form 28 joints, some with a great deal of motion and others with only a slight degree of motion. It is this flexible structure, under integrated muscular control that gives to the foot its ability to traverse any type of terrain or surface, without jarring or jolting the entire superstructure of the body. The flexibility inherent in such a structure is absolutely essential to a painless, graceful gait over any and all contours.

Modern civilization has made it necessary that man wear shoes. Shoes are constructed to conform to the structure of the normal foot. Any variation from the normal contour which produces a bony prominence may result in pressure and pain from the use of a shoe and immensely complicate the problem of obtaining foot gear.

With these facts in mind, the prime objectives of the treatment of fractures of the bones of the foot may be very simply stated. *They are two: first, stiffness or loss of flexibility must be minimized; second, bony prominences which will result in pressure from the use of a shoe must be avoided.* A perfect anatomical result does not necessarily insure that there will be flexibility. Indeed, all too often a perfect roentgenogram is seen, but the foot is so rigid that the individual cannot take a step without pain.

The pathological changes which occur in trauma to the foot are crushing, stretching, or tearing of ligaments, and fractures of bones. *These all result in hemorrhage which extravasates through tissue spaces and infiltrates the interstices of tissues.* The natural sequence of events is for the extravasated blood to clot, organize, and form fibrous tissue. This eventuates in dense intra-articular and extra-articular adhesions and fibrosis of ligaments, all of which severely interferes with the normal flexibility of the foot. This is accompanied by demineralization of bone and frequently leads to a syndrome, which has been described as "Sudeck's atrophy" or "reflex sympathetic dystrophy." Prolonged immobilization of a foot distended with blood is a very common precursor of this disabling syndrome.

A joint which allows normal motion is painless and useful. A joint in which there is no motion, because of bony ankylosis, is painless itself, but will seriously interfere with graceful activity and overtax adjacent articulations. A joint which is restricted in motion by adhesions but not ankylosed, will cause pain and disability when forced continuously to the limits of its restricted range of motion.

In the treatment of a fracture of any individual bone of the foot, the function of the entire foot must be constantly kept in mind. Attention must not be focused on the roentgenogram of a single bone and the rest of the foot and its part in weight bearing ignored, or the treatment may lead to prolonged, or even permanent disability, which could have been avoided.

FRACTURES OF THE ASTRAGALUS

Fracture of the astragalus which may be the most incapacitating of all fractures of the tarsal bones is fortunately not very frequent. This bone, which is situated between the leg

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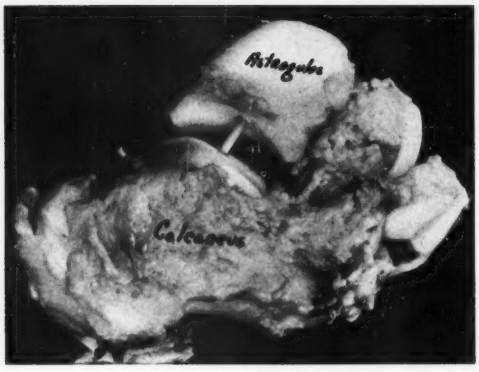

Fig. 1. Specimen of astragalus and calcaneus, showing large area of astragalus which is covered by articular cartilage. Its many articular surfaces enter into the ankle joint, the subastragalar joint, and the astragaloscaphoid joint. It is comparable to a kingbolt.

and the ankle, may be aptly compared to the kingbolt of a vehicle, keeping the wheels on the truck. The astragalus articulates with both the tibia and fibula at the ankle; with the os calcis where it permits lateral motion, and with the tarsal scaphoid, at which (Fig. 1) joint it permits rotational movement. Because of the many large articular surfaces at least 60 per cent of the surface of the astragalus is covered by articular cartilage. As a consequence of this, there is very little surface available for the entrance of blood vessels. *The astragalus has a very meager blood supply* (Fig. 2). Trauma of severe degree may result in a loss of circulation to a large portion of the astragalus, with resultant aseptic necrosis of the portion deprived of blood. This is to be expected, with a fracture through its neck when there is appreciable displacement of the body which requires manipulative or operative replacement.

A fracture through the neck of the astragalus is an exact counterpart of a fracture through the neck of the femur. Avascular necrosis of the proximal fragment of the fractured astragalus is a possible sequela in any fracture through the neck of the astragalus.

Aseptic necrosis of the body of the astragalus will result in (1) nonunion of the fracture of the bone; (2) loss of the ankle joint, and (3) loss of the subastragalar joint, which constitutes a total disability. If only anatomical replacement is carried out in a displaced fracture of the neck of the astragalus, this sequence of events may result (Figs. 3a and b, 4a and b).

Treatment of fracture of the astragalus demands prompt recognition of the type of fracture which may be followed by avascular necrosis of the major portion of the bone. If this type of fracture is recognized promptly, the ankle joint may be salvaged by carrying out a subastragalar fusion initially. The removal of the articular cartilage barrier between the os calcis and astragalus will permit new blood vessels to grow into the astragalus and preserve the articular cartilage on its superior surface, adjacent to the tibia, thus saving the ankle joint and greatly decreasing disability. Loss of motion due to bony ankylosis in the subastragalar joint can be tolerated well. Loss of motion in both the ankle and subastragalar joints is a major disability.

Fracture of the neck of the astragalus which is incomplete and in which there is no displacement will usually unite after adequate immobilization. The probability of aseptic necrosis of the body with deterioration of the ankle joint and subastragalar joint is not present in the incomplete or undisplaced fracture. Early subastragalar fusion is not indicated in such a fracture. Immobilization for as short a period of time as is required for bony union of the fracture by x-ray is adequate treatment.

Other less severe fractures of the astragalus occur which are in essence sprain fractures. An avulsion of the anterior capsule of the ankle and sprain fracture of the superior surface of the neck of the astragalus may result from plantar flexion forces. The posterior process of the astragalus may be fractured without displacement. Such minor fractures of the astragalus should be treated by measures aimed at the absorption of hemorrhage and early protected weight bearing. Prolonged immobilization to effect union of a minor fragment will lead to generalized stiffness in the remainder of the foot and increase disability.

Dislocation about the astragalus occurs occasionally. This usually consists of a displacement of the os calcis from under the astragalus, along with the scaphoid to the inner side of the foot, carrying the whole metatarsus medially (Fig. 5). The astragalus itself stays in

the ankle mortice. This is most often a closed dislocation but may be compound. Clinically, this dislocation may simulate an inversion fracture of the ankle, and only roentgenograms will show its true nature.

Subastragalar dislocations are not difficult to reduce when seen early and relaxing anesthesia is used. It may be necessary to insert a wire through the os calcis to obtain adequate traction to effect reduction. After reduction of the dislocation, the joints are stable due to their contours, and immobilization in plaster is not necessary for more than 3 to 4 weeks. There is always extensive hemorrhage in the soft tissues with this injury, and the proclivity for adhesions is great. Consequently, immobilization should be discontinued as early as possible. Some degree of permanent stiffness in the subastragalar and astragaloscaphoid joint commonly follows such an injury, but it can be minimized by discontinuing immobilization at an early date.

Astragalectomy, the removal of all or a part of the astragalus, may have an appeal to the uninitiated in some of these injuries. *When there is any possibility of replacement, even though comminution is severe, astragalectomy, total or partial, should not be done.* The loss of the astragalus causes severe crippling, and the absence of the substance of the astragalus greatly increases the difficulties of arthrodesis, or any type of reconstruction at a later date.

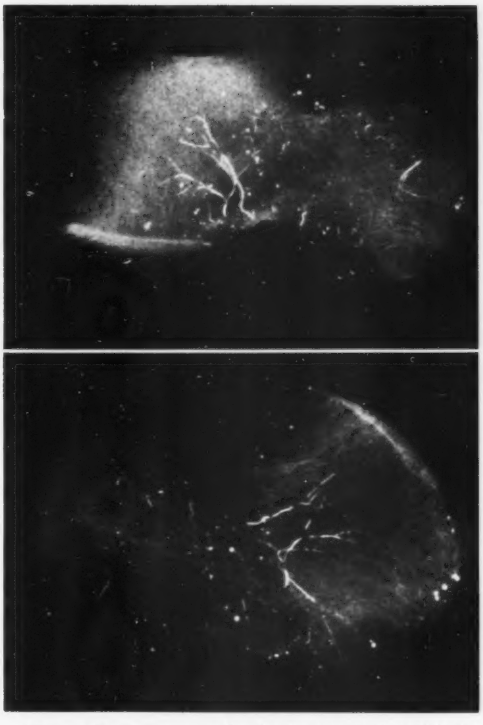

Fig. 2. Roentgenogram of excised astragalus in which the blood supply has been injected with radiopaque medium. Note paucity of injected material, particularly in posterior third of bone, indicating relative avascularity of the astragalus. a, above, Lateral view; b, posteroanterior view. (Fracture of the neck of the astragalus. McKeever, F. M. *Arch. Surg.*, 1943, 46: 720–735.)

FRACTURE OF THE TARSAL SCAPHOID

Fracture of the tarsal scaphoid, though a rare injury, requires special consideration. It is important in a bruised or contused foot not to mistake the presence of a supernumerary bone, known as the (os tibiale externum) accessory scaphoid, for a fracture. This accessory bone is present in 15 to 20 per cent of individuals. Knowledge of this developmental variation will prevent its being treated as a fracture (Fig. 6).

Sprain fractures of the scaphoid may result from pulling out of a portion of the insertion of the posterior tibial muscle. The entire insertion is practically never avulsed, as it has many slips. Such fractures should not be immobilized. They should be treated by measures to absorb hemorrhage; early motion and early protected weight bearing should be encouraged.

Severe fractures of the scaphoid result from strong compression forces. They result in a splitting of the scaphoid into two or more fragments, the splits radiating to the periphery of the bone, from the point at which the head of the astragalus compresses it. The articular cartilage of the head of the astragalus and the scaphoid is always severely damaged in this type of fracture. A fragment is extruded from between the astragalus and cuneiform to the medial or dorsal aspect of the foot. If the extruded fragment is not reduced it will produce a bony prominence. Shortening of the inner border of the foot also results if the fragment is left extruded.

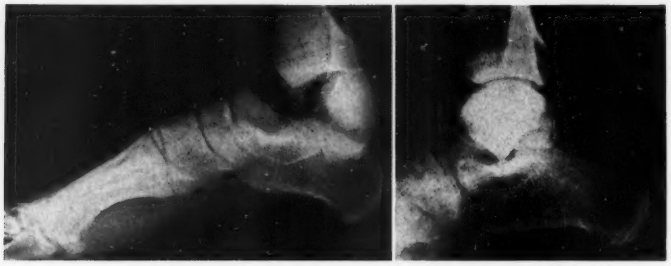

Fig. 3. a, left, Fracture of neck of astragalus with severe displacement, June, 1948. b, Roentgenogram of same fracture shown in a, 5 months (November, 1948) after anatomical replacement only. The fracture is not united, avascular necrosis of the posterior fragment has occurred, and the ankle joint space is beginning to narrow.

Treatment of the compression-extrusion type of fracture of the scaphoid requires reduction of the extruded fragments and maintenance of the fragment or fragments in their normal position between the head of the astragalus and cuneiform. The reduction is always unstable and extrusion tends to recur, even when the foot and leg are fixed in plaster (Figs. 7 and 8). Transfixion of the fragments by removable wires, skewering the reduced fragment to the cuneiform bones, or to the os calcis is often necessary to maintain satisfactory reduction.

Even with satisfactory reduction and union of the fragments, the aftermath of this fracture is severe. Because of the damage to articular cartilage at the time of injury, a severe traumatic arthritis of the astragaloscaphoid joint develops, with loss of rotational flexibility and pain.

FRACTURE OF THE CUBOID AND CUNEIFORM BONES

Isolated fractures of the cuboid or cuneiform bones seldom occur because of their protected and buttressed location in the metatarsus. When fractures do occur, they are caused by direct, crushing force and are a fissure or crush-compression type of fracture. There is little or no displacement and usually no reduction is possible or necessary.

The disability arising from these injuries is due to organization of extravasated blood and immobilization in plaster is ordinarily contraindicated (Fig. 9).

Treatment should be directed toward hastening absorption of blood, restoring normal circulation, the prevention of swelling and early motion. Early weight bearing, with the foot protected by adhesive strapping and cane or crutches should be instituted and normal weight bearing resumed as soon as it is not too painful to the patient.

FRACTURE OF THE METATARSALS AND PHALANGES

Injuries to the metatarsal bones may result in great disability. Damage which appears by x-ray as trivial may lead to severe crippling, and that which appears gross and irreparable in the roentgenogram may cause little or no disability. The crippling that follows what appears to be a minor injury and the often excellent recovery from an apparently severe injury is understandable when the anatomical and physiological relationship of the metatarsal bones to the rest of the foot is examined.

The first, second, and third metatarsal bones articulate with the three cuneiform bones. These articulations are very stable and there is no more motion at these joints than at the symphysis pubis. No position assumed by the foot in the most vigorous exercise produces motion in these joints. In fact, when great stress from trauma is applied to the ligaments of these joints, the result is not a rupture of the ligaments, but rather a fracture of the metatarsal or of the cuneiform bones, so rigidly are these bones bound together.

The base of the fourth metatarsal bone articulates with the cuboid bone and its parallel metatarsals. This joint permits slight up and down motion. The base of the fifth metatarsal

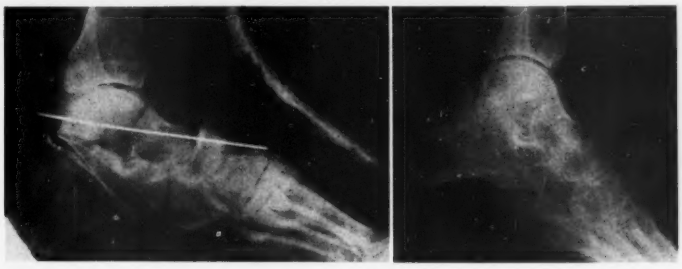

Fig. 4. a, left, Postoperative roentgenogram of fracture of neck of astragalus with displacement in which cartilage was removed from subastragalar and astragaloscaphoid joints and reduction maintained by internal fixation, to prevent deterioration ot ankle joint by allowing vascularization of astragalus. b, Roentgenogram of fracture shown in a, five months after subastragalar and astragaloscaphoid fusion. The fracture has united; there is no evidence of aseptic necrosis and the ankle joint space is normal in appearance.

articulates with the cuboid bone and the fourth metatarsal. This articulation permits considerable up and down spring. The situation is analogous to the hand. The carpometacarpal articulation of the index and middle finger is quite stable, and permits practically no movement. The carpometacarpal articulation of the ring and fifth fingers, however, permits of moderate up and down motion. This flexibility at the bases of the fourth and fifth metatarsal bones is necessary to smoothness in the gait since the fifth metatarsal head bears weight before the other metatarsal heads (Fig. 10).

The metatarsals articulate at their distal ends with the proximal phalanges. Walking requires great flexibility of the metatarsophalangeal joints. The degree of extension or dorsiflexion necessary at these joints for normal, comfortable walking is much greater than the degree of plantar flexion, and nature has provided a greater amount of this motion. This is particularly true of the great toe. Flexibility in plantar flexion of the metatarsophalangeal joints of the smaller toes is of great importance to allow the metatarsal heads to be released from pressure in weight bearing.

The interphalangeal joints are so constructed that their only motion is plantar flexion. This motion is important in the great toe for a smooth take-off. In the smaller toes it is of no great consequence and is frequently markedly diminished from confinement in a shoe.

There are certain sites in the metatarsal bones which carry a great threat of disability after injury, and there are other sites which can suffer extensive injury without probability of great crippling. These latter sites may be called silent areas. The danger points in order of their importance are: (1) the distal end of the first metatarsal bone, the metatarsophalangeal joint of the great toe, and the proximal end of the proximal phalanx of this toe; (2) the heads of the second, third, fourth, and fifth metatarsals and the metatarsophalangeal joints of these toes; (3) the articulation of the cuboid bone with the fourth and fifth metatarsals. Stiffness or restriction of motion may result in these vital joints without actual bony injury. Loss of flexibility is a common concomitant of immobilization in plaster and follows the treatment of any fracture of the lower extremity. *One of the most prolonged complaints of any patient following a fracture of the tibia or femur is pain in the foot, which is the result of stiffness from immobilization.*

The method of application of any cast which covers and immobilizes the toes, even though the pathologic condition requiring the cast is remote from them, is of great importance. Too often the toes are immobilized in a cast with the metatarsophalangeal joints in dorsiflexion and the metatarsal heads depressed. This results in rigid, depressed anterior arch, which requires a long period of time to become flexible. Any cast which immobilizes the metatarsophalangeal joints should have the transverse arch molded under the metatarsal heads so that if stiffness in the metatarsophalangeal

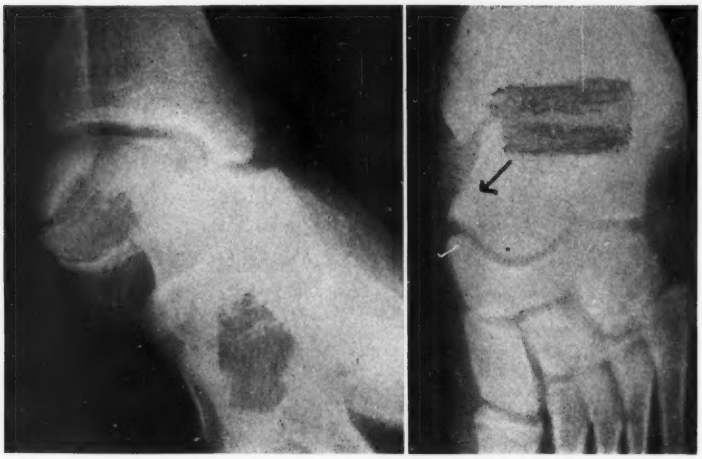

Fig. 5, left. Roentgenogram of dislocation of os calcis from under astragalus to medial side of leg, carrying forefoot with it.
Fig. 6. Roentgenogram of accessory scaphoid bone at arrow (os tibiale externum). This may be mistaken for fracture.

joints results, the second, third, and fourth metatarsal heads will not be points of pressure.

The proper management of injuries in this portion of the foot without severe bony damage never requires long immobilization in a cast. Contusions, sprains, and minor fractures without displacement should not be rigidly immobilized for long periods of time. The acute pain with these injuries comes from distention of the firm tissues by extravasated blood. When a foot with extensive extravasation of blood is immobilized in plaster for a long period of time the hemorrhage organizes, forms fibrous tissue, and eventually firm adhesions, which partially limit the free motion of the multiple joints of the foot and produce great pain in weight bearing. Demineralization of bone accompanies this and some permanent disability often ensues. These facts are the foundation for the so often heard statement that "a sprain is worse than a break."

Fig. 7. Roentgenogram of compression type fracture of tarsal scaphoid with extrusion of large fragment to dorsum of foot.

The treatment of acute injuries with extensive extravasation of blood and minor or negligible bony injury should consist, in the acute stage, of measures aimed at promoting absorption of the hematoma and prevention of swelling, followed by early protected weight bearing. The extremity should be elevated to minimize swelling and physical measures, such as heat or cold, and gentle effleurage applied to stimulate circulation. After the hematoma has decreased, protected weight bearing with a cane or crutch, and the foot taped, to prevent twists should be instituted. As soon as possible, the individual should begin normal weight bearing within the limits of pain. Examples of bony injuries which should be treated in this manner are the so called tennis fracture of the base of the fifth metatarsal bone, fractures of the metatarsal shafts without displacement, and fractures of the phalanges without displacement.

A fracture involving the head of the first metatarsal or the proximal phalanx of the great toe, may lead to serious disability, due

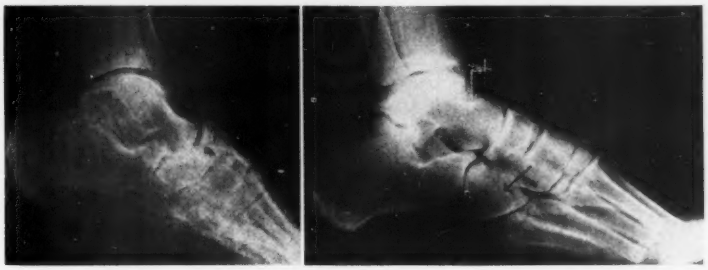

Fig. 8, left. Roentgenogram of malunited compression-extrusion fracture of tarsal scaphoid 5 years after injury. The fragment displaced after reduction. There are marked arthritic changes in astragaloscaphoid and scaphocuneiform joints.

Fig. 9. Roentgenogram of fissure fracture of cuboid. There is no displacement. Long immobilization is not indicated. Early weight bearing will minimize stiffness.

to loss of motion in the metatarsophalangeal joint. For comfortable walking, a very free range of dorsiflexion in this joint is necessary and any infringement on its arc will lead to pain. The impaired first metatarsophalangeal joint is termed "hallux rigidus." If the loss of motion in this joint is mild, it may not be too great a disability, and the pain from it may be relieved by stiffening the sole of the shoe. When dorsiflexion is severely restricted at the great toe joint, relief may be obtained by surgical measures (Figs. 11 and 12).

Operative measures for the correction of traumatic hallux rigidus have one purpose. That purpose is to create motion and all of the many procedures advocated are in the nature of an arthroplasty. The most widely applicable operation is the Keller bunionoplasty, in which a large portion of the proximal end of the proximal phalanx is resected. Thus, space is produced between the ends of the metatarsal and the remaining portion of the phalanx which leads to the formation of a pseudarthrosis and motion. The efficacy of this operation depends on the removal of adequate bone (Fig. 13).

Fractures of the smaller metatarsal heads, even though mild in degree, are of great import. A severe fibrotic change in the capsules of the small joints is prone to result after these injuries. The metatarsal heads are often displaced toward the sole of the foot. When union occurs in this position, the head of the metatarsal projecting into the sole will make weight bearing very painful.

The metatarsal head displaced into the sole of the foot must be corrected and placed in proper alignment with the shaft so that it is not a bony prominence in the anterior arch. This is often difficult. At times, it can be effected by digital pressure under the displaced head and manual traction on the toe. If this fails, continuous traction may be necessary. *Adhesive tape traction is a waste of time.* If traction is elected, it should be effected by a wire through the distal phalanx or pulp of the toe. Open reduction and internal fixation by intramedullary wire may be necessary to get the displaced head out of the sole of the foot. As soon as possible, motion of the toes should be started to avoid residual stiffness (Figs. 14 and 15).

Even though a good reduction is effected, stiffness may persist in the joint for a long period of time. When there is satisfactory position and healing, this stiffness will, as a rule, gradually yield to time and active use. During the period of stiffness, a Thomas bar on the sole of the shoe is an aid to the patient in walking, and anterior arch supports can be used later to great advantage.

In frank malunion of fractures of the metatarsal heads in which the head tilts downward and projects into the sole of the foot and stiffness persists, surgical intervention is indicated. The objective of surgery is to remove the bony mass projecting into the sole and produce a movable joint which will permit the distal end of the metatarsal to get away from the weight bearing skin of the sole. This can be accom-

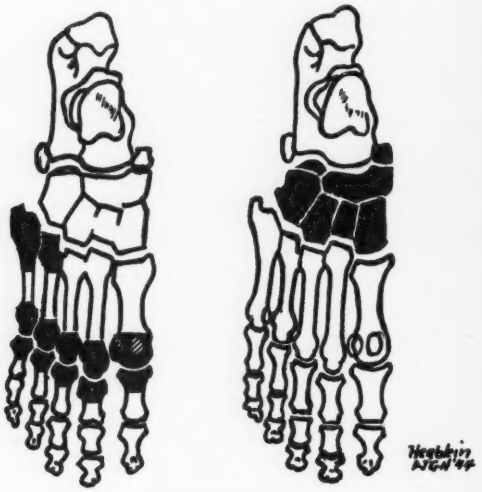

Fig. 10.[1] Diagram of metatarsal bones. a, left, Dark black areas indicate sites at which fractures of metatarsal bones result in disability from stiffness and deformity. These are vulnerable areas. b, Blackened areas indicate tarsal bones and show the keystone-like structure which permits of very little motion in metatarsocuneiform joints.

Fig. 11. Lateral roentgenogram of foot, flat and at end of normal step, showing degree of dorsiflexion necessary for comfortable gait at first metatarsophalangeal joint.

plished by generous resection of the involved metatarsal head and neck. This operation can be carried out with impunity on any or all of the 3 middle metatarsals. In a seriously deformed foot, it should be done occasionally on all the metatarsals. Occasionally, when stiffness is the principal factor and deformity is slight, the proximal phalanx of the toe may be excised, rather than remove the metatarsal head. If any dorsal angulation of the end of the metatarsal is present, this is inadvisable. The removal of the metatarsal heads can be accomplished easily from the dorsum of the foot, and an incision through the sole should be avoided. Patients who have had the metatarsal heads resected need a well fitting arch support. When only the first and fifth metatarsal heads remain, severe callosities will develop if the anterior arch is not protected by a support (Fig. 16).

Injuries of the base of the fourth and fifth metatarsal bones at this articulation with the cuboid bone are common. One of the most frequent fractures in the foot is the so called "tennis fracture" at the tuberosity of the fifth metatarsal. The tendon of the peroneus brevis muscle inserts on this tuberosity and an avulsion fracture is common. *This fracture is often overtreated.* Generally, displacement is negligible and this fracture should be treated by measures to absorb hemorrhage, adhesive strapping, and early weight bearing. Long immobilization in a cast to produce union leads to widespread stiffness. Severe displacement of the fragment may cause a bony prominence which is not well tolerated at this site on the foot. If this results, the bony prominence may require removal (Fig. 17).

From the twelfth to the sixteenth year of life, there may be a separate center of ossification or epiphysis on the lateral side of the base of the fifth metatarsal. Without knowledge of its existence, this may be mistakenly interpreted as a fracture and given unnecessary treatment.

[1]Figures 10 to 17 are from article by author, entitled "Injuries of the Forefoot," from Lectures on Reconstruction Surgery of the Extremities, 1944, Instructional Courses AAOS.

Fig. 12, a.

Fig. 12, b.

Fig. 13, a.

Fig. 13, b.

Fig. 12. Roentgenogram of fracture of distal end of first metatarsal which has healed, with marked traumatic arthritis of metatarsophalangeal joint and restriction of dorsiflexion.

Fig. 13. a, Roentgenogram of Keller operation with removal of proximal end of proximal phalanx, creating pseudarthrosis, for relief of traumatic hallux rigidus. b, Schematic drawing of operation. Shaded areas indicate bone removed.

If displacement in fractures in this area is severe, some stiffness is almost unavoidable. Occasionally a troublesome exostosis may result from displacement of a fragment. This can be removed surgically when healing is complete, and the troublesome nature is proved. No fragment in this area should be removed until healing has been complete, as in most instances no bony exostosis will result.

Fractures in the shafts of the metatarsals are not, as a rule, a cause of disability unless stiffness or deformity of the toes results, secondary to them. Even when fractures of the shaft result from tremendous force, displacement is not great because of the splinting action of the parallel bones. Fractures of the outer metatarsals, the fifth and first, also partake of this protection of the parallel structure. Rarely, one of the fragments may be displaced so that a bony prominence is present in the sole of the foot. When this occurs, the deformity must be corrected even though open reduction is necessary.

The second and third metatarsal shafts can be fractured without a history of definite trauma. Overstraining the foot from pro-

Fig. 14. Roentgenogram of fractures of the heads of the 3rd, 4th, and 5th metatarsal bones. The heads of the 4th and 5th metatarsals are displaced toward the sole of the foot and require correction. If they are left displaced, the result will be painful bony prominences in the sole of the foot.

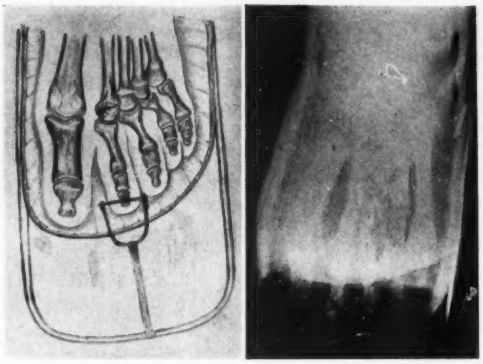

Fig. 15. a, left, Schematic drawing of traction applied by use of pin through distal phalanx to maintain reduction of displaced metatarsal head. b, Roentgenogram of traction applied to toes.

Fig. 17. Roentgenogram of fracture of base of 5th metatarsal without displacement. This fracture does not require immobilization in a plaster cast.

longed activity or ordinary walking may lead to an incomplete fracture of the shaft of a metatarsal without any displacement. Early after the onset of pain, the roentgenogram may not show this infraction or molecular fracture, and the cause of the pain may be obscure. After the elapse of 2 to 3 weeks, the roentgenogram will show the fracture line, due to demineralization at the ends of the fragment and may also show evidence of a fusiform mass of new bone about the fracture area. This mass has been mistaken for an osseous neoplasm and may result in unwarranted alarm. Because of its high incidence in soldiers in training, this type of metatarsal fracture has been named "march fracture." A knowledge of its possibility will prevent misinterpreting the roentgen picture as a neoplasm.

Fig. 16. Schematic drawing of foot in which 2nd, 3rd, and 4th metatarsal heads have been resected to relieve bony prominences in sole of foot.

In compound injuries of the metatarsal shafts with loss of substance, which appears irreparable, the prognosis is not too discouraging. Metatarsal bones have the average ability of regeneration, and the compactness of the area usually preserves some periosteum so that regeneration and repair are sometimes astounding. A large dehiscence in one or even two metatarsal shafts is not necessarily a great disability, as the remaining intact parallel bones preserve the general shape of the forefoot. The only deformity which follows is a slight retraction of the toes, whose metatarsals are involved. This is also true of the outer metatarsal shafts. Nonunion of fractures of the metatarsal shaft in the absence of a fragment projecting into the sole is not a cause of severe discomfort. Consequently, bone grafting operations to produce union, or operations to bridge large defects, are rarely indicated in the metatarsal bones. The stiffness resulting in the midtarsal region and the small joints of the toes secondary to the operative trauma

and long immobilization necessary after such operations is more disabling than the original condition. On rare occasions, a bone grafting operation may be indicated in the shaft of the first metatarsal bone.

In severe compound injuries of the forefoot, the same attitude should be taken as is taken toward the hand. Every effort should be made to save as much as possible. Every tissue with an adequate blood supply should be preserved. Promiscuous, lavish amputations should not be done if there is a reasonable chance of preserving the forefoot. This is as true of the great toe side of the forefoot as it is of the thumb. Frequently, minor operative procedures after healing will restore excellent function.

SUMMARY

The causes of disability following fracture of the bones of the foot are loss of normal flexibility, which is necessary to a graceful, painless gait, and bony prominences which cause pressure.

Minor fractures, without displacement, should not be subjected to long immobilization in casts. Rather, treatment should be directed to the absorption of the extravasated blood, restoration of normal circulation, early motion, and early weight bearing.

Certain fractures of the astragalus and scaphoid carry the threat of severe disability. These fractures require early recognition and appropriate treatment.

Reconstructive operations to produce motion and relieve stiffness will often decrease the disability which has resulted from fractures with deformity of the metatarsophalangeal joints.

Early radical amputation of all or part of a foot which has suffered a severe compound fracture is not justified. Recovery from such injuries is not infrequently surprisingly good.

ADENOLYMPHOMA
(PAPILLARY CYSTADENOMA LYMPHOMATOSUM)

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AMONG the rarer growths of the head and neck regions are those frequently designated as adenolymphoma or papillary cystadenoma lymphomatosum. Other terms that have been applied to these tumors are epitheliolymphoid cyst, branchioma, cylindrocellular branchiogenic adenoma, branchiogenous cystadenolymphoma, branchiogenic adenoma of lymph nodes, onkocytoma or oncocytoma, Warthin's tumor, and orbital inclusion adenoma (14, 26).

The term "epithelio" or related words should not be inserted into the title of this tumor because it tends to be confused with lymphoepithelioma, a tumor distinct from adenolymphoma, as described by Fein. Branchioma or branchiogenic should not be applied because there is no definite proof that they arise from branchiogenic remnants. Onkocytoma was the term applied by Jaffe, but this should be reserved for tumors composed of cells resembling the onkocytes, which have little or no lymphoid stroma, and adenoid formation is not a histological characteristic. Skorpil, and Ackerman each described an onkocytoma and independently suggested that the term should not be applied to an adenolymphoma. True onkocytomas have recently been described by Christopherson, and by Stump. Warthin described 2 cases of adenolymphoma in 1929, and his name has been applied to these tumors (14). However, he refers to 2 cases described by Albrecht and Artz in 1910. Regardless of priority, eponymous nomenclature seems undesirable. Kraissl and Stout's proposal that they be called orbital inclusion adenomas, based on a theory of origin from orbital inclusions has little factual support. We prefer the term adenolymphoma or papillary cystadenoma lymphomatosum because these are descriptive of the tumor. Adenolymphoma is favored because papillary ingrowths are not always a prominent feature of the tumor.

The adenolymphoma is reported as occurring in or near the salivary glands. They are not as rare as the approximately 108 recorded cases (15) would indicate. We wish to add 20 more cases and to discuss them. Ten of these tumors occurred in approximately 82,832 general surgical specimens at St. Luke's Hospital. Three hundred and seventy-five of these were of the salivary glands, including 177 mixed tumors of the parotid. The eleventh to the twentieth cases inclusive were from the Institute of Pathology within the Rhode Island Hospital.

PRESENTATION OF 20 NEW CASES OF ADENOLYMPHOMA

The youngest of the 20 patients was 42 years old and the oldest 78 years, with an average and a mean age of 60 years. Nineteen patients were males and 1 was a female. Fourteen tumors occurred on the right side, 4 on the left, 1 in the neck with the side not recorded, and 1 in the hypopharynx with no side recorded. Of the tumors on the right, 12 were in the region just posterior or below the angle of the mandible or posterior to the ascending ramus. The patient in Case 10, whose tumor was located in the most common site, is shown in Figure 1. Two were in the submaxillary region separate from the submaxillary gland. Of the tumors on the left, 2 were in the region just posterior or below the angle of the mandible, 1 below the ear, and 1 in the lateral neck. There were no bilateral or multiple adenolymphomas. In 11 cases, the tumor at operation or on microscopic examination was definitely in or adjacent to parotid gland tissue. In the 9 other cases the tumor was not proved to be in salivary gland tissue either at operation or microscopically. The 2 tumors in the submaxillary region were in the subcu-

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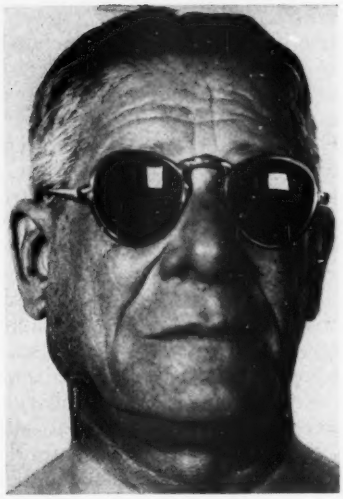

Fig. 1. Case 10. An adenolymphoma just posterior to the angle of the mandible, the most common site.

Fig. 2. Cross section of gross specimen from Case 7 showing large cyst and smaller multiloculated cysts. The more solid lower portion represents the usual gross appearance.

taneous tissue. The significance, if any, of the preponderance on right side is unknown.

Of the 19 adenolymphomas occurring in the cervical region the duration of symptoms was recorded in 17 cases. There was swelling for a period of from 2 months to 15 years with an average of 34 months. The adenolymphoma in the hypopharynx caused difficulty in swallowing for several days. The tumors usually increased slowly in size, but in 3 cases there was a sudden increase in size for several weeks. In Case 6 it was thought the swelling increased in size with an upper respiratory infection. Wendel also recorded such a case.

In 6 cases abnormal conditions were present elsewhere in the body. Three of these were malignant tumors, which we do not think is significant in this age group.

Excision was performed in 19 cases. The patient in Case 9, four months previous to excision, had an incision and drainage of a right submaxillary swelling which was thought to be an infected sebaceous cyst. This drained serous material until the time of excision. Laryngoscopy, esophagoscopy, and biopsy of the hypopharynx performed in Case 17 indicated the presence of an adenolymphoma of the hypopharynx. An associated carcinoma of the prostate and cerebral thrombosis were also present. He was free of any symptoms referable to his hypopharynx 6 months later.

No follow-up was secured in 7 cases. Thirteen cases were followed for a period of from 1 month to 12 years. There were no recurrences. In Case 9 excision of the adenolymphoma, sinus tract, and submaxillary gland was followed by a salivary fistula. This healed after excision of the fistula 2 years later. No adenolymphoma was found in the tissue removed with the fistula. No prophylactic radiotherapy has been given in any of our cases.

PATHOLOGY

On pathological examination the largest adenolymphoma excised was 10 centimeters in greatest diameter and the smallest one 1.5 centimeters in greatest diameter. On clinical examination they are smooth, elastic, and sometimes fluctuant. The skin is usually movable over the tumor, and the tumor is sometimes movable over the deeper structures. On pathological examination the tumor is usually reddish-tan in color, and there is a thin capsule of collagenous connective tissue. Plaut has found that they are not always completely encapsulated. They may contain cysts which

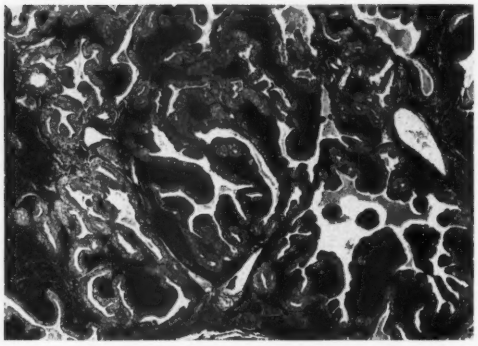

Fig. 3. Low power view in Case 4 showing the general arrangement of cystic spaces and the branched papillary processes of lymphoid tissue covered with epithelium.

are minute or several centimeters in diameter and contain clear, milky, or cafe-au-lait colored fluid. A picture of the gross specimen from Case 7 is shown in Figure 2.

On microscopic examination the cystic spaces are lined with pseudostratified columnar epithelium. Cilia were not definitely seen in our cases, although they have been reported as being present by other authors (3, 11, 18, 27, 30). Jaffe and Freshman and Kurland described intercellular secretory capillaries in the epithelium on special staining. We have not seen them in our slides stained by hematoxylin and eosin. The epithelium may form large papillary growths (Fig. 3) into the cystic spaces, while in some cases they are not conspicuous. The cells are tall columnar to cuboidal, with pink eosinophilic cytoplasm. The cytoplasm has a delicate network appearance when stained with eosin. The cells have a slightly swollen appearance. The nuclei are small and moderately dark staining, and arranged at two fairly regular levels, forming a double row (Fig. 4). This is quite similar to the lining of the ducts of salivary glands. The cells are based on a lymphoid stroma in which germinal centers can sometimes be seen (Fig. 4). No lymph sinuses are seen. Case 16, a 64 year old male, showed tubercles with giant cells, epithelioid cells, and caseation in the stroma suggesting tuberculosis (Figs. 5 and 6). There is no bacteriological proof available and no other focus of tuberculosis was to be found.

DISCUSSION

Seventy-six per cent of adenolymphomas occur in the 5th, 6th, and 7th decades (7). The youngest reported age is 2½ years (23), and the oldest 92 years (3). Both extremes were in males. The incidence of occurrence of male to female is quoted as 4.5:1 (7) to 10:1 (14). In our series the ratio was 19:1. In our cases the tumors tended to be on the right, but no particular laterality has been noted in the larger series in the literature (14).

Albrecht and Artz and Wendel have reported a total of 2 cases of adenolymphoma in the submaxillary gland. Our 2 cases in the submaxillary region were in the subcutaneous tissue, and not in the submaxillary gland. Martin and Erhlich believe that it fails to be appreciated that the tail of the parotid can lie in the submaxillary region. They question the authenticity of the cases of Albrecht and Artz and of Wendel of adenolymphomas in the submaxillary gland.

In Case 17 of our series the tumor occurred in the wall of the hypopharynx and it is, we believe, the first one recorded in that location in the literature. Photomicrographs are shown in Figures 7 and 8. Martin and Erhlich had a case which was retromandibular and beneath the sternocleidomastoid muscle, and which extended almost to the lateral wall of the pharynx. This is the nearest to the location of our Case 17 that we have found.

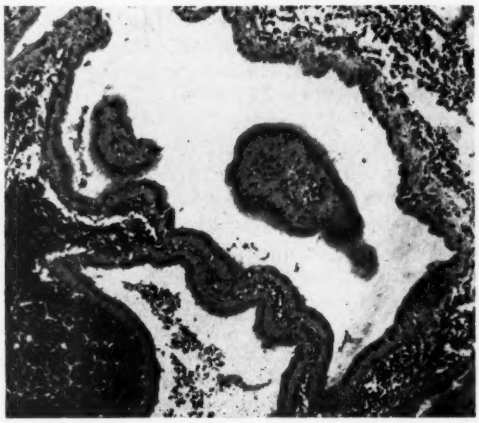

Fig. 4. Case 8. Typical structure of adenolymphoma. Notice the germinal follicle in the lymphoid tissue. ×89.

All of the tumors in our series were single. Cases of bilateral and multiple tumors have been reported. Ninō, Plaut, Martin and Erhlich, and Lederman report a total of 6 bilateral tumors. Ramage, Binnie, and McCall, and Martin and Erhlich report 3 cases of multiple tumors either homolateral, bilateral, or both homolateral and bilateral.

Our case of histological tuberculosis in the lymphoid stroma is rare. Two previous cases are reported, 1 by Lederman in a 12 year old boy and 1 by Owen in a 60 year old man. In Lederman's case a tuberculous cervical lymph node was removed from the same side 3 years later. All cases were from the region of the parotid or angle of the mandible. The surgical pathology files at St. Luke's Hospital contain 3 cases of tuberculosis of the parotid gland. Tuberculosis of the cervical lymph nodes is not rare. Therefore, it is not surprising to find it in this region in an adenolymphoma.

Five cases of malignant changes in an adenolymphoma are recorded in the literature (7, 12, 13, 22, 23). From the descriptions and photographs of Ssobolew's 1 case and Stohr and Risak's 1 case, there is a question as to their malignancy. This has been the opinion of other authors (7, 26). The third and fourth cases belonging to Gaston and Tedeschi and Lederman, respectively, showed metastatic lesions in the cervical lymph nodes. However, the primary type and site of the tumors were never proved. The fifth case was presented by Lloyd among 6 benign cases all of which were similar to Plaut's last 3 cases. These approached the morphology of an adenolymphoma, but were more typical of the lymphoepithelioma of Fein. In Lloyd's case the lymphoid tissue was replaced by a syncytial reticulosarcoma. This makes 5 cases of malignant tumor reported, 4 of carcinoma and 1 of sarcoma. The first 2 are of questionable malignancy, and the last 3 raise some question of their origin in an adenolymphoma.

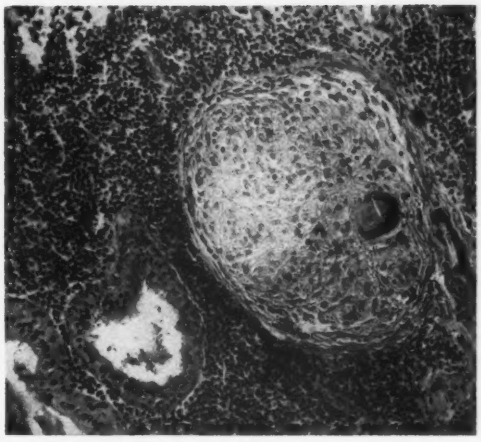

Fig. 6. Higher power of Case 16. Tubercle with giant cell, situated in lymphoid tissue of an adenolymphoma. Note the characteristic epithelium. ×90.

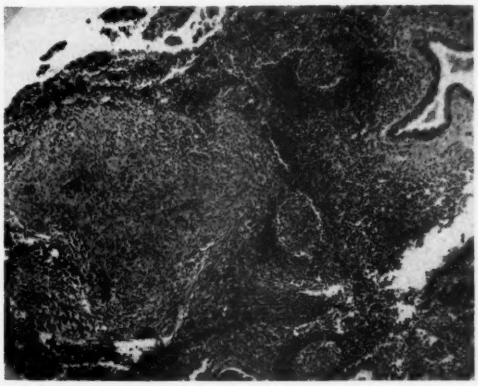

Fig. 5. Low power view of Case 16. To the left of the midline there is a large area of epithelioid cells with a small area of necrosis. In the right upper corner there is some epithelium.

HISTOGENESIS

Five main theories have been proposed for the origin of these tumors.

1. Heterotopic pharyngeal entoderm or salivary tissue in lymph nodes (Albrecht and Artz, 1910)
2. Branchiogenic remnants (Hildebrandt, 1898, and Ssobolew, 1912)
3. Heterotopic rests of entoderm of the eustachian tube or pharynx, with accompanying lymphoid tissue (Warthin, 1929)
4. From onkocytes (Hamperl, 1931, and Jaffe, 1932)
5. From orbital inclusions (Kraissl and Stout, 1933)

The theory that the adenolymphoma is derived from heterotopic rests of pharyngeal or

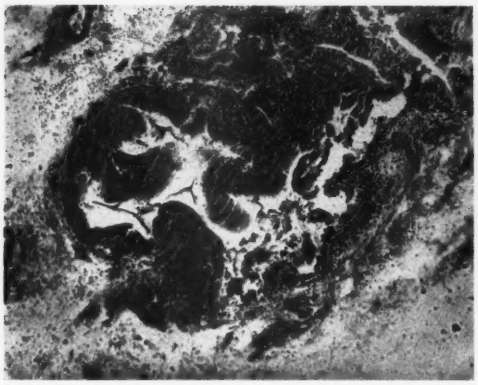

Fig. 7. Low power view of Case 17. The tissue was a biopsy of the hypopharynx.

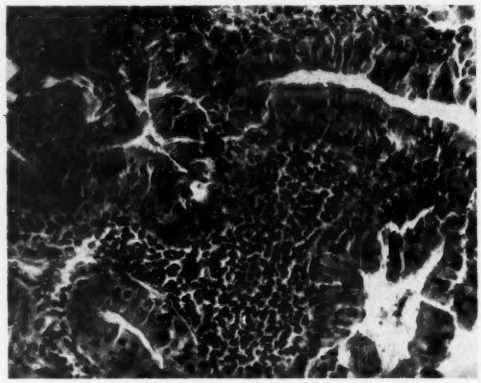

Fig. 8. A higher power view of Case 17, a biopsy of the hypopharynx. ×187.

salivary tissue in lymph nodes has been questioned by Jaffe and Martin and Erhlich. The latter authors could not find lymph sinuses and did not think that the lymphoid tissue resembled nodes. We could not find sinuses in our specimens, and do not think that the lymphoid tissue is in whole or in part a lymph node. Lloyd believes the lymphoid follicles are a reactive hyperplasia, the so-called "Flemming centers."

The onkocytes are cells which resemble the cells in the tissue in which they are found; but they have a densely staining eosinophilic network-like cytoplasm with hematoxylin and eosin stain, and are more turgid. They have been found in the salivary glands, anterior and posterior lobes and stalk of the hypophysis, thyroid, parathyroid, pancreas, liver, fallopian tubes, testes, and bronchial mucosa (8, 24). They are not found before the age of 20 years, but become increasingly prevalent after that age. Hamperl believed that the onkocyte represented a redifferentation or an aging of a particular cell, but not a degeneration. Stump has reviewed the origin of onkocytes. Adenolymphomas have been found only in the parotid region, submaxillary region, neck, and hypopharynx; yet the onkocytes are in other locations. Adenolymphomas have occurred under the age of 20 years, but the onkocyte has not been found below that age. The onkocytoma or onkocytic adenoma is a tumor distinct from adenolymphoma, as previously mentioned.

Kraissl and Stout proposed that the adenolymphoma arose from a remnant of the orbital inclusion. The orbital inclusion is a salivary gland in the infraorbital fat of carnivorous animals with ducts emptying near the upper molar teeth. Freshman and Kurland presented a case of the tumor at the anterior border of the sternocleidomastoid muscle. They objected to the orbital inclusion theory because the inclusion is situated anterior to the parotid gland, while the tumor was posterior. The orbital inclusion theory does not explain the position of the adenolymphoma in the hypopharynx in Case 17.

An origin from rests of branchiogenic entoderm or heterotopic rests of eustachian tube or pharyngeal entoderm with its accompanying lymphoid tissue appears to us to be the most tenable, knowing full well that the more known about a tumor the more likely it is to be taken out of the category of an embryonic rest. We favor the opinion of Warthin that it originates from eustachian tube or pharyngeal entodermal rests, because it closely resembles the pseudostratified columnar epithelium of these regions. Branchiogenic cysts are usually lined by stratified squamous, stratified columnar, and ciliated or nonciliated columnar epithelium. Sebaceous glands, hair follicles, or cartilage may be present in a branchiogenic cyst. There may be some areas of stratification in an adenolymphoma, but the predominant feature is the pseudostratified columnar epithelium. No sebaceous glands, hair follicles,

or cartilage have been reported in the adenolymphoma group. We, therefore, favor without conclusive evidence the origin of adenolymphoma from ectopic pharyngeal or eustachian tube entoderm.

TREATMENT

The tumor was excised in 19 of our 20 cases. There were no recurrences. There was 1 complication, a salivary fistula, which was later excised. The adenolymphoma of the hypopharynx was not excised, only a biopsy specimen being removed; the patient had no further difficulty in swallowing. Surgical excision is the treatment of choice and is recommended for mechanical and cosmetic reasons, and because of the possibility of malignant transformation. There were no injuries to the facial nerve. The branches of the nerve run over the capsule. Recurrences have been reported in the literature when the excision was probably incomplete (3, 12). Lederman has treated a patient with incomplete removal of the tumor in the parotid region, by radium implantation; and a second patient with a recurrence and an adenolymphoma which had been subjected to biopsy on the opposite side, both in the parotid region, by external radium radiation. The 3 tumors disappeared in the 2 cases. Tillinger gave preoperative radiation.

We believe excision without radiation to be adequate and the treatment of choice.

SUMMARY

1. The terminology of adenolymphoma is reviewed.

2. Twenty new cases are added to the approximately 108 recorded cases. One case of adenolymphoma of the hypopharynx is reported.

3. The pathology and histogenesis is reviewed.

4. Surgical excision is the treatment of choice and gives good results.

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CONSTRUCTION OF A SUBSTITUTE BLADDER AND URETHRA

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IN the treatment of some tumors of the bladder, prostate, rectum, and uterus as well as in certain congenital anomalies, and other conditions, it is necessary to divert the urinary stream. Numerous operations have been designed to make life livable as well as possible after urinary diversion. Rubin's recent article makes any further review of the literature unnecessary. In general, these procedures fall into the following categories: (1) cutaneous fistulas; (2) implantation of the ureters into some portion of the gastrointestinal tract left in continuity, ureterosigmoidostomy being most acceptable; (3) formation of an artificial bladder from the ileocecal region with the appendix serving as a fistula; (4) formation of an artificial bladder from an isolated segment of sigmoid with urethral continuity or with direct cutaneous fistulas.

Each of these procedures has value and each has some limitation such as soiling, stricture formation, recurrent pyelonephritis, incontinence, or a limitation of the extent of surgery possible when dealing with tumors.

We wish to present a procedure for the formation of a substitute bladder with the following advantages:

1. There is no chance of contamination by the fecal stream.

2. The ureteral anastomoses are easily made and can be covered on all sides by peritoneum without tension and without pull as a result of peristalsis.

3. The ureters need not be mobilized for more than 3 to 4 centimeters.

4. The ureteral orifices can be examined and dilated if need be through a cystoscope.

5. A bag should not be necessary to prevent leakage.

From the Presbyterian Hospital. Funds for this investigation were obtained from the Otho S. A. Sprague Memorial Institute Fund of the Presbyterian Hospital and the Rice Cancer Fund of the Presbyterian Hospital.

This bladder is made from the isolated cecum and ascending colon. The urethra is formed by the terminal ileum. Bowel continuity is re-established by an ileocolostomy. The ureters are transplanted into the cecum.

Mann, Bollman, and Puestow showed that an isolated piece of small intestine anastomosed in an antiperistaltic manner between the skin and the gastrointestinal tract in the dog, allowed no fecal spillage if the antiperistaltic segment was more than 4 to 6 inches long. The principle has been used in the Roux Y anastomosis to correct biliary stricture (Cole *et al.*). Pearse found that the antiperistaltic arm should be 12 inches long to prevent regurgitation of intestinal contents. This action serves as part of our cutoff valve. The ileocecal valve is competent and prevents reflux of bowel contents from the cecum into the ileum in an appreciable percentage of cases of large bowel obstruction. This action serves as the second factor to help make our cutoff valve.

Numerous animal experiments have shown that reabsorption from an isolated loop of cecum or sigmoid need not be feared if drainage is provided (1, 7). Gallo reported 1 patient who lived 13 years after implantation of both ureters into an isolated cecal pouch. The urinary tract was essentially normal at death.

Before this operation was attempted on a patient it was performed on several dogs. The procedure is much more difficult in the dog than in man because the dog has a straight colon which is more difficult to mobilize. It is also much more difficult to prepare the bowel, which resulted in more cases of peritonitis than would be expected in man.

The surgery was usually done in two stages. At the first stage 4 to 6 inches of cecum and appendix with a variable length of the terminal ileum attached was isolated. An ileo-

colostomy was then performed to re-establish continuity. The end of the terminal ileum was then brought out through a stab wound. This pouch of ileum, cecum, and appendix was irrigated with a suspension of sulfadiazine for 2 to 3 weeks before attempting to transplant the ureters. The Coffey I method of ureteral anastomosis was used with the exception of 2 cases in which the Nesbit elliptical direct anastomosis was done.

Dog 1. On April 11, 1949 the new bladder was made; 3 weeks later the left ureter was transplanted by use of the Coffey I method. The dog was catheterized once daily through the ileal opening. The substitute bladder was completely continent and held up to 180 cubic centimeters of urine. The preoperative nonprotein nitrogen was 37. The right ureter was implanted 4 weeks after the left. The new bladder still contained hair and had not been irrigated with sulfadiazine. There was considerable soiling. The substitute bladder remained continent. The dog was usually catheterized twice daily. One week after the second ureteral implant the nonprotein nitrogen was 66. The dog died 11 days after the second implant.

The autopsy showed a massive peritonitis. There was no urinary leakage. The ileal urethra was 7 inches long. The right kidney and ureter, the site of the most recent transplant, showed a moderate degree of dilatation. The left ureter and kidney were grossly normal. The inside of the substitute bladder was pale and soft. The necrotic swollen tip of the right ureter was still present inside the bladder which probably accounted for the dilatation on that side.

Microscopic study of the cecum and appendix showed that the superficial mucosal glands had sloughed away but the deeper glands were everywhere intact. There were no changes in the muscular layers. A ring of new bone formation was found around the left ureteral orifice; there was no apparent stricture (Fig. 1).

Dog 6. The preoperative nonprotein nitrogen was 33. On June 28, 1949 the new bladder was made. The ileum was about 5 inches long. Three weeks later both ureters were transplanted. Eighteen days later the nonprotein nitrogen was 51 and the bladder capacity was 180 cubic centimeters. At this time catheterization was employed three times a day. Intravenous pyelogram showed a slight ureteral dilatation and hydronephrosis. Five weeks after implantation the nonprotein nitrogen was 60 and the bladder capacity was 250 cubic centimeters, and a week later it was 360 to 400 cubic centimeters. There was overflow incontinence when this was exceeded. The increased capacity followed a return to once daily catheterization. The phenolsulfonphthalein test showed excretion of 60 per cent in half an hour. Three and a half months after transplantation the nonprotein nitrogen was 26 and the dog was well on once daily catheterization. He died 4½ months after ureteral anastomosis. The cause is unknown.

Fig. 1. Dog 1. The opening of the left ureter into the cecum showing ring of bone formation.

The autopsy showed that the ureters and kidneys were grossly normal. The ureteral orifices were not strictured. The inside of the substitute bladder was free of the heavy mucoid secretion which had been present in the other animals. Inside the bladder a piece of Pezzer catheter was found. It was heavily encrusted with inorganic salts. Some pieces of black silk suture were dangling inside the bladder. These also had calcium encrustations. There was no sign of peritonitis. The heart and lungs were normal.

Our animal experiments showed that a substitute bladder and urethra made in this way is continent up to the capacity of the bladder. If the animal is not catheterized regularly and often enough to prevent back pressure several things may happen. In one, overflow leakage never occurred and the animal finally died as a result of back pressure since he was catheterized only once a day. In another, infrequent catheterization in the presence of a

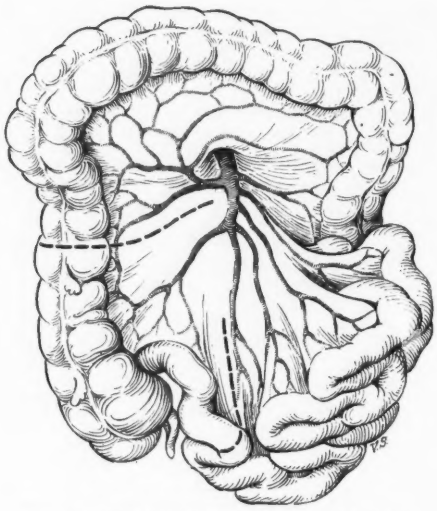


Fig. 2. Dotted lines indicate the lines of incision.

small initial capacity of the bladder caused dribbling with a gradual rise of nonprotein nitrogen and a gradual increase in the size of the artificial bladder and, finally, death due to hydronephrosis and infection. If the animal could survive the back pressure needed to dilate the bladder to a size sufficient to hold an entire day's urinary output, then he seemingly could survive with a normal nonprotein nitrogen and phenolsulfonphthalein result even on once a day catheterization.

The experiments convinced us that such a bladder would probably be continent. With a larger bladder we could expect that a patient who could catheterize himself sufficiently often to prevent back pressure might be expected to do well.

Our first patient was a 63 year old white male who had had 5 different operations elsewhere for a leiomyosarcoma of the perirectal tissues between July 1947 and our first examination in September 1949. An abdominoperineal resection had been performed in July 1947. He had an extensive recurrence in the perineal wound. There was no evidence of distant metastasis and Doctor George Hass, our pathologist, predicted that this tumor would extend slowly, would be more or less encapsulated, and would have almost no tendency to distant metastasis. On this basis an attempt was made to remove it by excising the lower end of the sacrum. The tumor was found to be localized and sharply demarcated except in the region of the base of the bladder and prostate where obviously it had become invasive. For this reason further surgery was abandoned. He was offered the possibility of a cure, first, by the construction of a new bladder and urethra and then by removal of the involved bladder and prostate through the posterior wound.

TECHNIQUE OF OPERATION

Preparation. The bowel was prepared in the following manner for 6 days: sulfasuxidine, 2 grams, 4 times a day; milk of magnesia, 1 ounce, at night; 1½ pints water enema, twice a day; high caloric low residue diet.

A Harris tube with suction was passed into the small bowel the night before surgery in order to diminish contamination at operation.

On October 13, 1949 the substitute bladder and urethra were formed and bilateral ureterocecal anastomosis was done. At the operation a 0.5 centimeter nodule was found in the old abdominal scar which proved to be a tumor implant. There was another nodule in the mesentery of the terminal ileum about 5 inches proximal to the ileocecal valve which required resection of some of the blood supply when it was removed. This proved to be scar and not tumor. No other evidence of tumor was found within the abdomen.

The midline colostomy was dissected free and covered with a rubber dam. After removal of the two nodules described the right colon and appendix and terminal ileum were mobilized widely. An appendectomy was performed. The ascending colon was then divided between rubbershod clamps just below the hepatic flexure (Fig. 2). (Hereafter we shall make this segment of cecum larger.) Both ends were turned in with a layer of continuous catgut suture for the mucosa and two layers of continuous silk for the muscularis and serosa. The terminal ileum was divided about 9 inches proximal to the ileocecal valve, the distal end was covered with rubber dam and the proximal end was closed as in the colon. A lateral anastomosis was then done between the ileum and right transverse colon. From this point on we felt that we could interrupt our procedure at any time if the condition of the patient warranted it.

The advantage of using the right side of the bowel as a bladder was immediately evident.

The ileocolic artery has an independent segmental vascular bed and allows for sufficient mobility so that such a bladder may be anastomosed to both ureters almost at the kidney pelves if desired (Fig. 3). The bowel is larger here, and there are rarely any diverticula to make anastomosis difficult or to act as a threat of leakage because of infection.

Both ureters were bound down in tight scar at and above their crossing of the iliac arteries. The right ureter was dissected free starting 1½ inches below the pelvic brim. It was not dilated. It was divided about 1 inch below the iliac artery, the distal end was ligated with silk and turned below the pelvic floor. The new bladder was now rotated so that the hepatic flexure end of the new bladder extended to the left and the ileal urethra extended to the right, *with the ileocecal valve lying anteriorly. The right ureteral anastomosis should be done first.* If done secondly, the anastomosis will have to be done through or behind the blood supply.

The ureteral anastomoses were made in the posterior part of the cecum. The excess right ureter was excised and, at most, 1½ inches of ureter had to be mobilized from its bed. The ureter was transplanted *transversely* to the long axis of the bowel (Figs. 4, 5, and 6). This allowed great mobility and extraperitonealization sufficient to satisfy the most meticulous surgeon. A modified Coffey I technique was used, with the tunnel about 1 inch long. The end of the ureter was split longitudinally for about ¼ inch and the fishmouth ends were now pulled into the bowel by a single fine chromic catgut stitch through each. These stitches passed through the bowel wall beyond the end of the incision so that the end of the ureter was held wide open and the open end was about ¼ inch beyond the end of the incision through the mucosa. The tunnel was closed over with interrupted atraumatic silk stitches. The posterior peritoneal flaps which had been split to mobilize the ureter were then loosely covered over the ureter and the anastomosis. In this manner, the area of anastomosis was completely covered with peritoneum and the new bladder was now firmly anchored to the posterior peritoneum (Figs. 7 and 8).

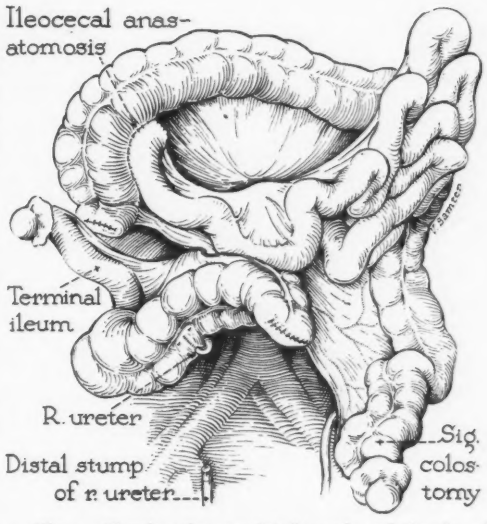


Fig. 3. Showing the completed pouch and the site of implantation of the right ureter.

The left ureter was dilated to about twice normal size. It was implanted into the new bladder exactly as was done on the previous side. The new bladder now lay in a kidney shape, draped about the mesentery of the terminal sigmoid colostomy. The bladder was secured to the posterior parietal peritoneum by interrupted sutures.

The ileal urethra was about 9 inches long. It was brought through a stab wound on the right after it had been fixed by stitches in a gently curving direction from the ileocecal valve to the abdominal wall.

Two small drains were placed near the ureteral anastomoses. The terminal sigmoid colostomy was brought out through a left stab wound. The midline wound was closed with continuous catgut sutures and numerous through-and-through button tension sutures (Figs. 9 and 10).

An indwelling catheter was left in the new bladder for 1 week. Urinary output was 1,500 cubic centimeters or more daily. There was no leakage of urine even when the catheter became blocked with mucus as it often did in the first few days. On the first such occasion 300 cubic centimeters of urine drained as soon as the mucus was removed from the catheter.

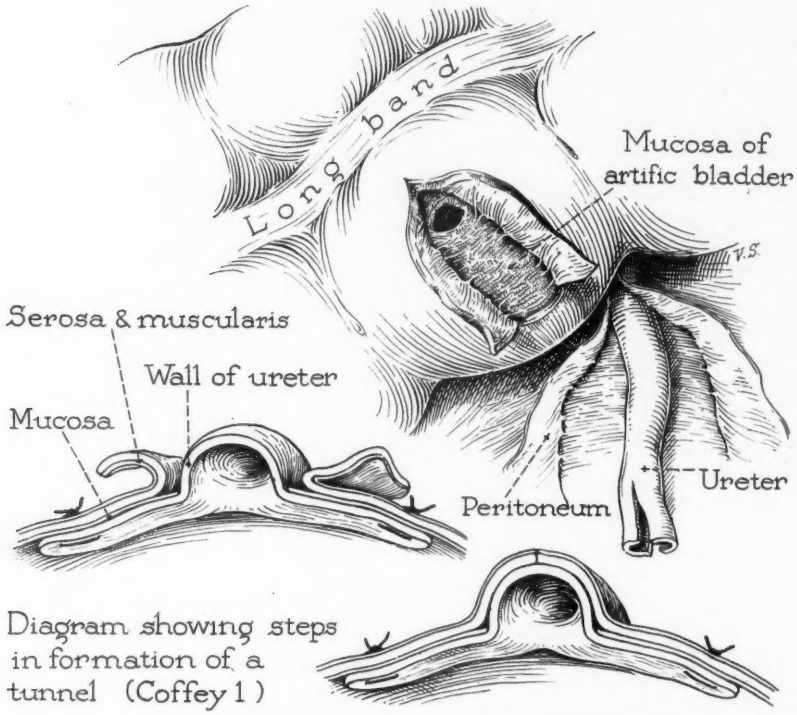


Fig. 4, above. Shows the preparation of the mucosal tunnel made transverse to the long axis of the bowel and the fishmouthing of the ureteral end. The ureter is brought up from behind the segment of cecum. This requires a minimal mobilization of the ureter.

Fig. 5, left below. Shows the fixation of the ureter in the tunnel, the stitches being placed about a quarter of an inch distal to the opening in the mucosa so that the opening in the ureter is pulled inside the bowel when the catgut stitches are tied.

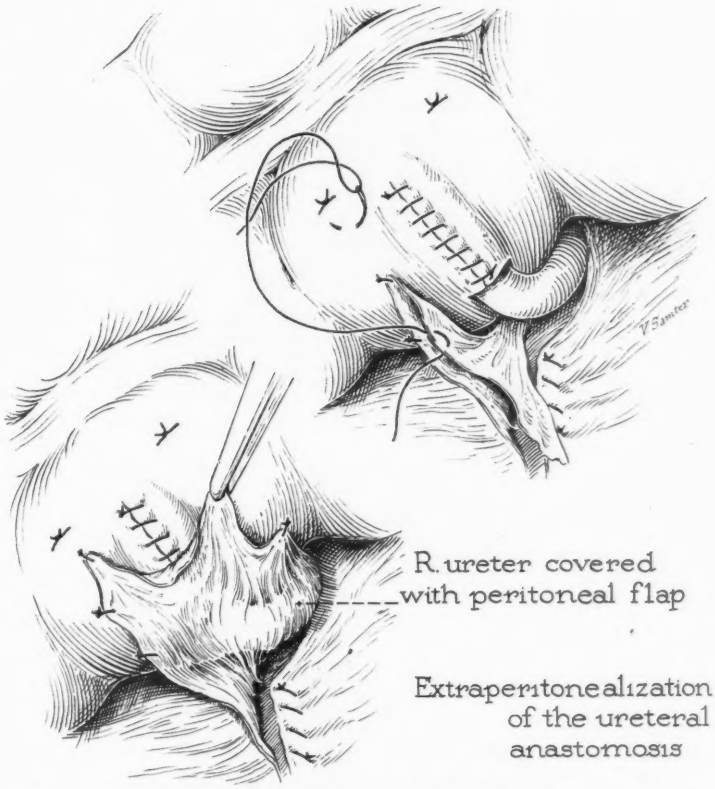
Fig. 6, right below. Closure of the muscularis and serosa of the bowel over the ureter.

On October 15, 1949 the nonprotein nitrogen was 27. He had an uneventful recovery, the nasal tube was removed on the 3rd postoperative day. His maximum temperature was 100.6 degrees and he was no more of a problem than the average patient with an abdominoperineal resection.

After a week the catheter was removed at times. He would leak urine after a time. It was evident that we should have made a larger bladder or would have to wait for gradual dilatation.

It became increasingly difficult to replace the catheter in the bladder as there seemed to be a sharp turn developing in the course of the urethra.

On the night of the 16th postoperative day the catheter which had been placed in the bladder at night fell out and he awakened in the morning with a tightly distended bladder into which we were unable to pass a catheter. No urine leaked after 16 hours. He developed a feeling of tightness in the abdomen but no other sign. An attempt to pass a catheter under vision through a cystoscope was impossible because of a sharp kink about 4 to 5 inches from the skin. For this reason it was decided to open the abdomen about the new urethra and correct the stricture. A right rectus incision was made which finally had to be 5 inches long. We found that a small abscess had formed between the posterior lateral



Figs. 7, above, 8, below. Illustrates the manner of making a peritoneal tunnel which will enclose the anastomosis. After this is finished the substitute bladder is firmly fixed to the parietal peritoneum by interrupted silk stitches.

abdominal wall and the area where we had removed the nodule of scar tissue from the mesentery of the ileum about 4 to 5 inches proximal to the ileocecal valve. This contained granulation tissue with little pus. It had gradually angulated the bowel. The terminal ileal urethra beyond this abscess was resected. The remaining urethra was about 4 inches long. This was brought out through the incision so that there was a straight 4 inch passage from the skin through the ileocecal valve. A catheter was placed into the new bladder. The abdomen was closed with interrupted silk. He had a bowel movement the next evening and was disturbed no more than one having an appendectomy. His nonprotein nitrogen on November 2, four days after this procedure, was 23.

On November 19, 1949 the distal segments of the ureters, the bladder, the prostate, the urogenital diaphragm, and the pelvic tissue from the iliac vessels downward were resected. The patient received 1,000 cubic centimeters of blood during this procedure which was not particularly difficult. The wound was packed with a rubber dam. The patient had a fever of 99.4 that day and none thereafter. He took fluids by mouth starting 24 hours after the operation. He was out of bed in 48 hours. He is doing surprisingly well. The bladder capacity is now about 210 to 220 cubic centimeters. The serial excretory uro-

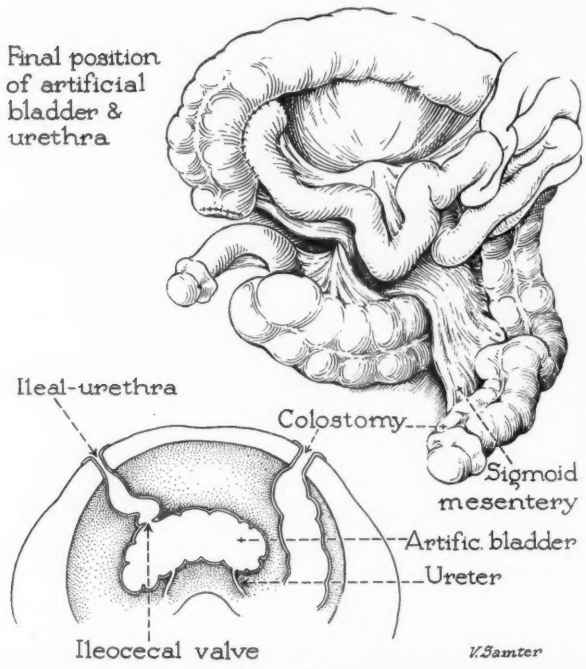


Fig. 9, above. Final position of the substitute bladder and urethra when there is a sigmoid colostomy as in this case.

Fig. 10, below. Cross section of the body at the level of the body at the level of the substitute bladder, urethra, and opening of the terminal colostomy. The diagram shows why the ureteral orifices were easily visualized through the cystoscope.

grams on the 27th and 47th postoperative days showed mild dilatation of the ureters and pelves. On the 56th postoperative day a cystoscope was easily passed into the bladder. The bowel mucosa was normal in appearance. Indigo carmine, 5 cubic centimeters, was injected intravenously. Both ureteral orifices were easily identified and could have been catheterized without difficulty.

The surgical specimen showed two thumb sized nodules of tumor still sharply demarcated, involving the base of the bladder and the prostate. One of these was very close to the trigone. There was no other sign of tumor so that we feel that there is some chance of permanent cure.

DISCUSSION

Of course, it is too early to tell whether there will be trouble with stricturing at the ureteral anastomoses. It may be that a different type of anastomosis will be necessary.

If signs of stricturing at the ureteral anastomoses develop it is our hope that one or both orifices can be seen through a cystoscope passed through the ileocecal valve. With the type of modified Coffey I anastomosis shown here, it should be safe either to dilate the stricture or actually to incise the strictured area on the cecal side as in a ureteral meatotomy. If severe hydronephrosis and infection should follow such a stricture and if it is impossible to correct through a cystoscope, there would be little risk in opening the anterior wall of the cecal pouch through the abdomen and correcting the stricture as described.

If one wished, it would be very simple to do the Coffey II procedure and bring the ureteral catheters out through the ileal stoma. This procedure allows one to do a ureteral implant

with a minimal amount of mobilization of the ureters and with the possibility of completely surrounding the anastomotic sites with peritoneum. When the ureters are transplanted in a transverse direction to the long axis of the bowel there is a much better chance of healing primarily as peristaltic action is less apt to cause movement of the ureter in its tunnel when the cecum is firmly fixed to the posterior peritoneum.

The new bladder should be larger than we have made this first one. The bowel should probably be divided so as to give a bladder about 7 to 8 inches in length if dilatation with its possibility of back pressure is to be avoided. However, it will probably be found that the smaller bladder can be dilated without much risk, if it is done more gradually than was the case in our dogs. There has been a good deal of mucus secreted by the bladder. This is gradually diminishing. The experience of Gallo has shown that absorption from a bladder made of cecum will not be a problem at least if there is a free urinary fistula. We feel that the same condition holds here.

The resection of pelvic structures can be carried out at the same time or as a second stage operation without disturbing the new urinary system.

The control of the urine will depend on the size of the bladder and on the competency of the ileocecal valve. It will also depend on the degree of antiperistaltic action which may prove to be insufficient with a 4 to 5 inch segment. If the bladder is large to begin with, or if it gradually dilates, it will not tend to leak until it is filled. If leakage occurs there are several ways it can be controlled. A bag similar to a Koenig-Rutzen ileostomy bag would work. The simple insertion of a catheter into the bladder, the end being passed into a collapsible rubber bag or condom, the whole lightly strapped to the abdomen would suffice. A Foley catheter can be passed into the bladder, inflated, and the urine drained into a suitable receptacle.

SUMMARY OF STEPS IN THE PROCEDURE

1. A description of the preoperative preparation is presented.
2. Exploration is carried out.
3. Terminal ileum, cecum, and right colon are thoroughly mobilized. Appendectomy is performed if it has not been done previously.
4. The right colon is divided near the hepatic flexure and the divided ends are closed so as to make an artificial bladder which is 5 to 7 inches in length.
5. The terminal ileum is divided about 5 to 6 inches proximal to the ileocecal valve with thorough mobilization of the blood supply to this new pouch of ileum and cecum.
6. Anastomosis of ileotransverse colon is performed to re-establish intestinal continuity. After this is done the operation can be terminated at any time if the condition of the patient warrants it or if the bowel is not well cleaned.
7. The new bladder is rotated so that the hepatic flexure end lies to the left and the ileal urethra lies to the right with the *ileocecal valve lying anteriorly*.
8. The *right ureter* is mobilized for 1 to 1½ inches proximal to the end of the new ureter. The ureteral end is fishmouthed and the right ureter implanted into the posterior surface of the cecum by a modified Coffey I technique. The ureter then should enter the bowel in a direction at right angles to the long axis of the bowel. This ureteral anastomosis is then covered with peritoneal flaps which give added protection. The right side of the pouch is now securely fixed to the posterior parietal peritoneum to prevent motion.
9. The same type of ureteral anastomosis is performed on the left, by carrying the end of the new bladder either below the mesentery of the terminal colostomy, if there is to be one, or through the mesentery of the left colon if the bowel continuity is to be preserved.
10. If a colostomy is made, it should be brought out through a left stab wound.
11. The terminal ileum is brought out through a right McBurney's incision or through a stab wound and is fixed in such a manner that the new urethra will be in a straight line to the ileocecal valve and also so that the new urethra will enter the new bladder anteriorly. This urethra should not be angulated. We believe that a 5 inch urethra will serve, but it may be necessary to make it longer.

12. Eradication of the pathology in the pelvis can be done at the same time or as a second operation. Or only the right ureter may be anastomosed at the first operation and the left ureter can be implanted at the second operation when the pelvic tissues are removed.

13. After operation the new bladder should be kept decompressed.

14. After recovery the patient will need to insert a catheter into the bladder often enough to prevent overfilling. If there is leakage, a skin tight bag can be used or a catheter with an inflatable cuff can be inserted to prevent leakage.

NOTE.—Since this article was accepted for publication we have found that Dr. Eugene Bricker, St. Louis, had previously successfully performed a similar operation on some patients. They have done well. No attempt was made to establish continence—a Koenig-Rutzen bag was used to collect the urine.

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EDITORIAL

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JUNE, 1950

BRAIN TUMORS

DEFINITE progress has been made in the localization and removal of brain tumors since the first successful removal by R. J. Godlee in 1884 of a tumor which A. H. Bennett localized by neurologic studies. The accumulated experience since then has given a better understanding of brain tumors, the symptoms they produce, and methods for their removal. Physical aids have been developed which assist in the localization and distinction of cerebral lesions.

In the diagnosis of an organic intracranial lesion, it is extremely important to proceed in an orderly manner by the careful taking of the history and by the conducting of a general, neurologic, ophthalmologic, roentgenographic, and selected laboratory and special diagnostic examinations.

A thoroughly elicited history of the patient's complaints, with a general examination, assists in distinguishing between coexisting diseases and the early symptoms of increased intracranial pressure which are characterized by headache, vomiting, and choked optic discs. Headache in ambulatory patients occurs daily in the early morning hours and frequently awakens the patient about 4 a.m. Vomiting is of the projectile type, and is often associated with headache and with movements of the head. Pain in the occipital region associated with rigidity of the neck is an accompanying symptom of infratentorial tumors. Papilledema and choked optic discs develop when the free flow of cerebrospinal fluid is impaired by an expanding lesion within the cranium. However, choked optic discs may result from other lesions, such as retrobulbar neuritis, intraorbital tumors, hydrocephalus, and inflammatory lesions of the meninges and brain.

All patients with symptoms that suggest the presence of a cerebral lesion should be given a thorough neurological examination. Symptoms produced by brain tumors vary according to their origin, position of the tumor, rate of growth, size, and pathologic features. Each tumor produces a chain of symptoms peculiar to its own life cycle. It is apparent that lesions of the frontal lobes will give rise to psychic and personality changes. Those arising in the speech and motor centers will produce aphasia, apraxia, jacksonian and grand mal convulsions, increased reflexes, monoplegia, and hemiplegia. Other symptoms develop as respective centers, nuclei and tracts become invaded or destroyed or deprived of their normal blood supply. Certain tumors, such as those situated in the sella turcica or in the chiasmal region and in the cerebellopontine angle, may give rise to symptoms of localization before symptoms of increased intracranial pressure are manifested.

Ophthalmologic examinations reveal the presence or absence of choked discs, optic atrophy, disturbance in ocular movements, nystagmus, and defects in perimetric fields. These findings are extremely valuable in the localization of and distinction between intracranial lesions.

Roentgenographic studies of the heads of patients who are suspected of having an intracranial lesion are a necessity in order to complete the examination. Flat roentgenograms made in the lateral and anteroposterior positions, with an occasional set of stereoscopic roentgenograms, will reveal evidence of increased intracranial pressure by the presence of convolutional markings in the calvarium and destruction of the clinoid processes. Local evidence of a tumor is presented by an enlargement of the sella turcica, erosions or hyperostosis of the skull and by deposits of calcium in a neoplasm or vascular lesion.

Routine laboratory tests are employed much as they would be employed in completing a thorough general examination. Spinal puncture studies should be avoided in the presence of choked optic discs, since herniation of the brain may take place through the tentorial notch or the foramen magnum, with a resulting fatality.

Special examinations and diagnostic aids are available, but they should be used only when necessary to complete a diagnosis or make a differential diagnosis of a cerebral lesion. Pneumoencephalography and pneumoventriculography are procedures in which the cerebrospinal fluid is removed and replaced by air or oxygen. The pneumoencephalogram is made by effecting an exchange of cerebrospinal fluid and oxygen through a spinal puncture in the lumbar area, and is employed only when there is no evidence of choked optic discs. The pneumoventriculogram is made by making trephine openings in the parietal bones over the posterior horns of the lateral ventricles and by the introduction of a brain cannula into the ventricles. After the cerebrospinal fluid has been removed and replaced with oxygen, a series of roentgenograms are made. Since the air or oxygen is less dense than cerebrospinal fluid, the films will reveal the outlines of the ventricles and subarachnoid spaces. Displacement or distortion of the ventricles or subarachnoid spaces suggests the presence of an expanding lesion, internal hydrocephalus, or cortical atrophy.

Electroencephalography is one of the newer procedures employed in the localization of brain tumors. The purpose of an electroencephalogram is to enable the diagnostician to determine whether or not the normal brain waves have been disturbed by a neoplasm. Present knowledge of electroencephalography makes it a reasonable aid in the differential diagnosis, although it is not infallible.

Roentgenographic studies of cerebral circulation with a contrast medium (diodrast) have become very useful in distinguishing lesions within and about the brain. Some neurosurgeons prefer to employ angiography to pneumoencephalography, since they believe the sequelae appear to be less frequent.

Certain dyes such as fluorescein, which has a special affinity for neoplastic tissue, have been injected intravenously just prior to operation in order to enable the surgeon better to visualize the boundaries of infiltrating gliomas. Moore and others have been able to combine an isotope with fluorescein in such a way that when the combination is injected intravenously, it has a tendency to concentrate in a cerebral neoplasm, thus making it possible to detect a brain tumor by the use of a Geiger counter. Dye studies carried out independently or in combination with the isotopes are still in the investigative stage.

Tumors developing within the cranium usually are referred to as "brain tumors," even though they arise from structures other than the brain. However, they all produce neurologic symptoms sooner or later. Tumors that develop from (1) the meninges are fibroblastomas, meningiomas, and sarcomas; (2) tumors arising from special structures are pituitary adenomas and pinealomas; (3) tumors arising from heterotopic rests are epidermoids, dermoids, and craniopharyngiomas; (4) tumors developing from cranial nerves are neurofibromas; (5) tumors arising from vascular tissues are angiomas and hemangioendotheliomas; (6) tumors arising from neural elements are gliomas in varying degrees of malignancy; and (7) still other lesions are metastatic malignant neoplasms.

The fact that many tumors are circumscribed, benign, and encapsulated makes it possible to remove them. Then, too, radical resection of gliomas which arise in silent areas of the brain often provides temporary relief of many months' duration. Irradiation therapy is also effective in ameliorating the symptoms produced by vascular tumors.

Surgical techniques have become reasonably well standardized, although they may vary slightly to suit the individual surgeon. No longer do we find long dissertations in the literature on methods of controlling hemorrhage and elevating osteoplastic flaps. The usual anesthesia is one which employs inhalation. Ether is administered on the open mask over a McGill intratracheal tube. Occasionally, a local anesthetic agent is indicated, as is also avertin anesthesia. Scalp bleeding is controlled with scalp clips or by the application of pointed forceps to the galea. The bone flap is cut with a Gigli saw. Bleeding from bone is controlled by the use of Horsley's wax. Meningeal and cortical bleeding is controlled by silk sutures, silver clips, and electrocoagulation. Removal of a tumor is effected by elevation of the tumor *in toto* or by the fractional method, in which a wire loop is employed through which runs a high frequency desiccating current. Coagulant agents such as oxidized cellulose, can be used to control capillary bleeding from cut surfaces. Rarely is the use of a soft-rubber tissue drain indicated. Bone flaps as a rule are wired in place with tantalum wire. Trephine openings are closed with tantalum buttons. The scalp is closed with silk sutures. Surgical shock is prevented by the intravenous injection of fluids, such as isotonic solution of sodium chloride, 5 per cent solution of glucose, and by the transfusion of blood when such treatment is needed.

The real problem that confronts the neurosurgeon today is not craniotomy, but that of surgical management of the brain tumor.

ALFRED W. ADSON.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

THE treatise edited by Warren Cole entitled *Operative Technic in Specialty Surgery*[1] was designed particularly for the general surgeon and should be accorded an enthusiastic reception. With the present tendency toward multiplication of the surgical specialties and the tendency for these specialties subsequently to assume an autonomous status, the residency programs of today are apt to leave the general surgeon somewhat lacking in experience in one or more of these surgical fields. Moreover, due to the rapid growth and increase in the scope of the surgical specialties new techniques and therapeutic methods are developing with such rapidity that even the experienced surgeon finds it difficult to follow and evaluate the newest and most recent advancements. In order to meet this situation, the editor has attempted to present in simple form descriptions of selected surgical procedures which have now become reasonably well standardized and which are generally accepted in surgical practice. He has enlisted the aid of 21 contributors, each a well known authority in his particular field. The result is a well balanced and well integrated book which serves as a fitting sequel to the volume on general surgery published previously.

The subject matter includes plastic surgery, thoracic surgery (including intrathoracic cardiovascular disorders), orthopedic surgery, neurosurgery, gynecology, and male urology. The section on plastic surgery deals first with the fundamental problems of wounds and wound healing, followed by detailed accounts of the various types of skin grafts, with their indications and contraindications while specific directions are given for their use. The definitive reparative procedures described are those which are most commonly employed in the correction of deformities due to burns or injury as well as certain of the simpler congenital deformities. This chapter is handsomely illustrated with halftone drawings, which add greatly to the value of the text.

The chapters devoted to thoracic surgery include brief descriptions of the basic anatomy and physiology of the thorax followed by the therapeutic measures utilized in the management of trauma and infection. The techniques of thoracoplasty, pulmonary resection and diaphragmatic hernia are covered in considerable detail. In the field of cardiac surgery, methods of resuscitation and treatment of heart injury and pericarditis should be of interest to all readers. Probably few general surgeons will at present wish to attempt the operations for patent ductus arteriosus, malformations of the heart and great vessels, revascularization of the heart or pulmonary embolectomy.

Considerable space is devoted to orthopedic surgery. An entire chapter concerning surgical approaches to the various joints is one of the features of this section. It is profusely illustrated and the descriptions are accurate and precise. The material is well organized and outlined which should make it readily available for quick reference. Osteomyelitis, musculoskeletal deformities, and neoplasms of bone are also considered. In the chapter on fractures the the author stresses the use of conservative methods whenever possible but includes adequate descriptions of operations for those fractures which are now generally acknowledged to be treated best by open operation. The descriptions are well illustrated by appropriate roentgenograms of actual cases, but they lack the accompanying illustrations, diagrams, or drawings so essential for a full comprehension and proper understanding of operative procedures.

In the neurosurgical section, the chapter covering surgery of the head emphasizes especially those conditions resulting from trauma and infection, although a reasonable amount of space is devoted to a discussion of brain tumors. The drawings from the pen of Ralph Sweet are outstanding. Chapters on the spinal cord, cranial nerves, and peripheral nerves follow. The latter should be especially valuable for those who are engaged in the surgery of trauma. The section dealing with the autonomic nervous system should be popular since it describes in considerable detail the steps of the several procedures now commonly employed in the treatment of hypertension and peripheral vascular disease. Liberal use has been made of line drawings which amplify greatly the material presented in the text.

The chapter on gynecological surgery will be of particular interest to the general surgeon. The authors state that only those surgical procedures which in their experience have proved most useful have been included. Repetition is thereby eliminated and confusion avoided by the deletion of outmoded and seldom used operations. The radical hysterectomy for carcinoma of the cervix revived and popularized by them is fully described step by step. Illustrations in this section are limited to simple diagrams which fail to give the impression of third dimension. Because of this, the presentation loses some of its effectiveness.

[1] OPERATIVE TECHNIC IN SPECIALTY SURGERY. Edited by Warren H. Cole, M.D., F.A.C.S. Introduction by Allen O. Whipple, M.D., F.A.C.S. New York: Appleton Century Crofts, Inc., 1949.

To the pure specialist much of the subject matter may seem elementary, whereas for the general surgeon for whom it was primarily designed, it should be of inestimable value and the editor and collaborators are to be congratulated on the general excellence of their work. This book should be especially helpful to resident surgeons and others during their training period and likewise to those general surgeons in practice who from time to time by choice or necessity are required to cross the conventional boundaries into adjoining surgical fields.

HENRY K. RANSOM.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

GENITO-URINARY SURGERY. By Sir John Thomson-Walker, D.L., M.B., C.M. (Ed.), F.R.C.S. (Eng.). Edited and revised by Kenneth Walker, M.A., M.B., B.C. (Cantab.), F.R.C.S. (Eng.), T.I.C.S. 3d ed. New York, London: Paul B. Hoeber, Inc., 1950.

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THROMBOSIS IN ARTERIOSCLEROSIS OF THE LOWER EXTREMITIES. By Edward A. Edwards, M.D., F.A.C.S. Springfield, Ill.: Charles C Thomas, 1950.

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CLINICAL CONGRESS OF AMERICAN COLLEGE OF SURGEONS

FREDERICK A. COLLER, Ann Arbor, *President*
HENRY W. CAVE, New York, *President-Elect*

PRELIMINARY PROGRAM FOR THE 36th CLINICAL CONGRESS—HOTEL STATLER, BOSTON OCTOBER 23 TO 27, 1950

THE thirty-sixth annual Clinical Congress of the American College of Surgeons will be held in Boston October 23 to 27. The Fellows of the College and the hospital personnel of the Boston area will sponsor an extensive program of operative clinics and demonstrations covering all phases of surgical and hospital activity.

Mechanics Hall will house the extensive exhibit of medical and hospital supplies and equipment, television and medical motion picture showings, registration for surgeons and hospital representatives, and a few of the sessions. The other sessions will be held in the Hotel Statler, Copley-Plaza Hotel, John Hancock Auditorium, and Symphony Hall.

Boston was host to the Clinical Congresses of 1915, 1922, 1928, 1934, and 1941. Notable contributions to surgical and medical knowledge were made at these meetings. Those who will attend in 1950 may anticipate a program of broad scope and interest, for the surgeons of Boston have complete facilities at their command in the three medical schools and the thirty or more approved hospitals in Boston and vicinity.

CLINICAL PROGRAM, INCLUDING TELEVISION

Under the leadership of the Committee on Arrangements, and the hospital representatives whom they have appointed, a program of operative and nonoperative clinics is being arranged in 24 hospitals, as a major feature of the Clinical Congress. Visiting surgeons will have every opportunity to obtain first hand information on a wide variety of surgical and related subjects. Specialists in varied fields, as well as surgeons, will participate so that many subjects will be considered from different viewpoints.

Color telecasts of surgical procedures at one of the hospitals will be shown daily during the Congress, and the Committee is considering other black and white television possibilities. The television will unquestionably be a great attraction at the 1950 Clinical Congress, as it has been at the last three in New York, Los Angeles, and Chicago.

OFFICIAL MEETINGS

A meeting of the Governors of the College is planned on Sunday afternoon, October 22. They will also meet for luncheon on Wednesday.

Dr. Frederick A. Coller of Ann Arbor, the outgoing President, will deliver the Presidential address at the Presidential Meeting on Monday evening. At the same session Dr. Henry W. Cave of New York will be installed as President, and Dr. Warren H. Cole of Chicago and Dr. G. Gavin Miller of Montreal as First and Second Vice President respectively. The Presidential Meeting is scheduled for the Ballroom of the Statler Hotel.

The annual Convocation which includes formal initiation ceremonies for the new Fellows will take place on Friday evening, October 27, probably in Symphony Hall.

The Annual Meeting of Fellows will be held on Thursday afternoon.

EVENING SCIENTIFIC SESSIONS

Eminent surgeons and specialists, recognized as authorities in their fields, will address the scientific meetings which will be held on Tuesday, Wednesday, and Thursday evenings. The preliminary program for the general surgery sessions follows:

Tuesday, October 24

The Concept of the General-Adaptation-Syndrome as Applied to Surgical Problems (with

Special Emphasis upon Cortisone and ACTH). HANS SELYE, Montreal

Biophysics in Surgery. AMBROSE STORCK, New Orleans

The Principles Involved in the Clinical Use of Streptokinase-Streptodornase. WILLIAM S. TILLETT, New York

Wednesday, October 25

Fracture Oration. (Selected by Committee on Trauma)

Intravenous Fat Feeding. FREDERICK J. STARE, Boston

The Neurological Complications of Spinal Anesthesia. R. D. DRIPPS, Philadelphia

Thursday, October 26

Lobotomy Versus Other Operations for the Relief of Pain. JAMES C. WHITE, Boston

The Etiology and Treatment of Hirschsprung's Disease. ORVAR SWENSON, Boston

Late Surgical Complications Following Irradiation of Pelvic Viscera. WILLIAM CRAWFORD WHITE, New York

On Tuesday and Thursday evenings, there will be separate sessions for Ophthalmology and for Otorhinolaryngology. The programs will be announced later. The Wednesday evening meeting will be a joint ophthalmology and otorhinolaryngology session with the New England Otolaryngological Society participating.

AFTERNOON PANEL DISCUSSIONS

General surgery panel discussions will be held Monday through Thursday afternoons from 1:30 to 3:00 o'clock, and Monday through Wednesday afternoons from 3:30 to 5:00 o'clock. The subjects will be as follows: Monday, 1:30, "Transthoracic Approach to Subdiaphragmatic Lesions"; 3:30, "Cancer of the Uterus"; Tuesday, 1:30, "Anesthesia"; 3:30, "Reconstructive Surgery of the Hand"; Wednesday, 1:30, "Surgical Treatment of Congenital Anomalies of the Digestive Tract"; 3:30, "Pitfalls in Surgery of the Gallbladder and Biliary Ducts"; Thursday, 1:30, "Acute, Nontraumatic Conditions in the Abdomen."

Ophthalmology panel discussions will be held Tuesday, Wednesday, and Thursday afternoons from 1:30 to 3:00 o'clock. The subjects will be as follows: Tuesday, "Chiasmal Syndrome"; Wednesday, "Diagnosis of Orbital Tumors"; Thursday, "Selection of Operative Technic in Retinal Separation."

Otorhinolaryngology panel discussions will be held Tuesday and Thursday afternoons from 3:30 to 5:00 o'clock. The subjects will be: Tuesday, "The Pre-School Deaf Child"; Thursday, "The Management of the Vertiginous Patient." On Wednesday there will be special otorhinolaryngology clinics in the morning and in the afternoon a panel discussion from 2:00 to 5:00 o'clock on "Fenestration for Otosclerosis." This all day program will be held jointly with the New England Otolaryngological Society.

Friday afternoon will be devoted to panel discussion sessions for six special fields of surgery as follows: orthopedic surgery, plastic surgery, urological surgery, thoracic surgery, neurological surgery, and obstetrics and gynecological surgery.

FORUM ON FUNDAMENTAL SURGICAL PROBLEMS

The Forum on Fundamental Surgical Problems will be held again in 1950 to give special opportunity for the presentation of the newest discoveries resulting from research, particularly by the younger surgeons. Brief reports of original clinical and experimental observations relating to the broad aspects of surgery and the surgical specialties will be given. A large number of abstracts have already been received from which selection for presentation will be made by the Committee, of which Dr. Owen Wangensteen of Minneapolis is the chairman.

SYMPOSIA ON CANCER AND ON TRAUMA

Because of the widespread interest in these special fields, a Symposium on Trauma is being planned for one afternoon, and a Symposium on Cancer for another afternoon. As in former years, these sessions are expected to attract a large attendance.

MEDICAL MOTION PICTURE PROGRAM

The Medical Motion Picture Committee is now choosing films which are to be shown at the Clinical Congress. Films which have been recently produced should be forwarded to the College for immediate review as it is the policy to include in the Clinical Congress program only those films which were submitted in time to obtain approval by the Committee on Medical Motion Pictures. The showings of medical motion pictures at the Clinical Congress are one of the leading attractions and are well attended.

HOSPITAL CONFERENCES

The twenty-ninth Hospital Standardization Conference will convene during the first 4 days of the Clinical Congress. Its opening meeting will constitute the first formal session of the Congress and will be for both surgeons and hospital representatives. Hospital administrators, trustees.

members of medical staffs, nurses, technicians, dietitians, and heads of the various hospital departments and their personnel, are invited to participate in the discussions at the conferences which will be directed by leading authorities in the hospital field.

COMMITTEE ON ARRANGEMENTS

The Boston Committee on General Arrangements for the Clinical Congress is composed of the following Fellows:

THOMAS H. LANMAN, *chairman*
DONALD MUNRO, *vice-chairman*
ORVAR SWENSON, *secretary*
ARTHUR W. ALLEN, *chairman*, Board of Regents
Other members of the Executive Committee:
J. ENGLEBERT DUNPHY, LANGDON PARSONS, and C. STUART WELCH

EDWIN W. CAVE
EDWARD D. CHURCHILL
FLETCHER H. COLBY
EDWIN B. DUNPHY
ROBERT E. GROSS
FRANK H. LAHEY
CHARLES C. LUND
LELAND S. MCKITTRICK
JOE VINCENT MEIGS
CHARLES G. MIXTER
FRANCIS D. MOORE
WILLIAM R. MORRISON
DUNCAN E. REID
LEROY A. SCHALL
REGINALD H. SMITHWICK

HOSPITALS AND HOSPITAL REPRESENTATIVES

The hospitals which will arrange clinics for the 1950 Clinical Congress, and the names of the hospital representatives, follow:

HOSPITAL	REPRESENTATIVE
Beth Israel Hospital	Dr. Howard A. Frank
Boston Lying-In Hospital	Dr. Paul Gustafson
Carney Hospital	Dr. John J. Todd
Chelsea Naval Hospital	Dr. Henry W. Hudson
Children's Medical Center	Dr. William A. Elliston
Cushing Veterans Administration Hospital	Dr. Henry Faxon
Faulkner Hospital	Dr. Marshall K. Bartlett
Free Hospital for Women	Dr. Christopher J. Duncan
Malden Hospital	Dr. Clement Lynch
Massachusetts Eye and Ear—Ophthalmology	Dr. Henry A. Mosher
Massachusetts Eye and Ear—Otolaryngology	Dr. Francis L. Weille
Massachusetts General Hospital	Dr. Howard Ulfelder
Massachusetts Memorial Hospital	Dr. George Whitelaw
Mount Auburn Hospital, Cambridge	Dr. Joseph Tartakoff
New England Baptist Hospital	Dr. Herbert D. Adams
New England Center Hospital	Dr. Wyland Leadbetter
New England Deaconess Hospital	Dr. Herbert D. Adams
New England Deaconess Hospital—Palmer Memorial Unit	Dr. Clifford Franseen
New England Hospital for Women and Children	Dr. Felicia Banas
Newton-Wellesley Hospital, Newton Lower Falls	Dr. Richard I. Smith
Peter Bent Brigham Hospital	Dr. Thomas B. Quigley
Pondville Hospital, Walpole	Dr. Richard Wallace
Robert Breck Brigham Hospital	Dr. Theodore A. Potter
St. Elizabeth's Hospital	Dr. John Spellman
Veterans Administration Hospital—West Roxbury	Dr. Frederick Ross

ADVANCE REGISTRATION

Surgeons who wish to attend the Clinical Congress should register in advance. Advance registration will greatly expedite the procedure of registering. No registration fee will be charged Fellows whose dues are paid to December 31, 1949. For endorsed Junior and Senior Candidates, the fee will be $5.00. Non-Fellows who after individual consideration are permitted to register will pay a fee of $10.00. No registration fee will be required of initiates of the class of 1950.

HOTEL RESERVATIONS

It is desirable to make hotel reservations as early as possible. In making these, communications should be addressed to the Convention Bureau of the Boston Chamber of Commerce, 80 Federal Street, Boston 10, which will start booking reservations on June 1. It is important that you state that you will be attending the Clinical Congress of the American College of Surgeons. All hotel reservations, both for surgeons and hospital representatives, are to clear through the Convention Bureau. No correspondence should be sent directly to the hotels. A form for reservations will be enclosed in a letter to Fellows. Choice of hotels may be designated.

In addition to the headquarters hotels, the Statler and Copley-Plaza, there are a number of first-class hotels within a short distance of headquarters. The following hotels are recommended:

	Minimun Rate with Bath	
	Single	Double
Bellevue	$ 4.00	$ 6.00
Bradford	5.00	7.00
Copley-Plaza	5.00	7.70
Kenmore	5.00	9.00
Manger	4.00	5.50
Parker House	4.50	7.00
Somerset	6.00	10.00
Statler	5.00	8.75
Touraine	4.50	7.00

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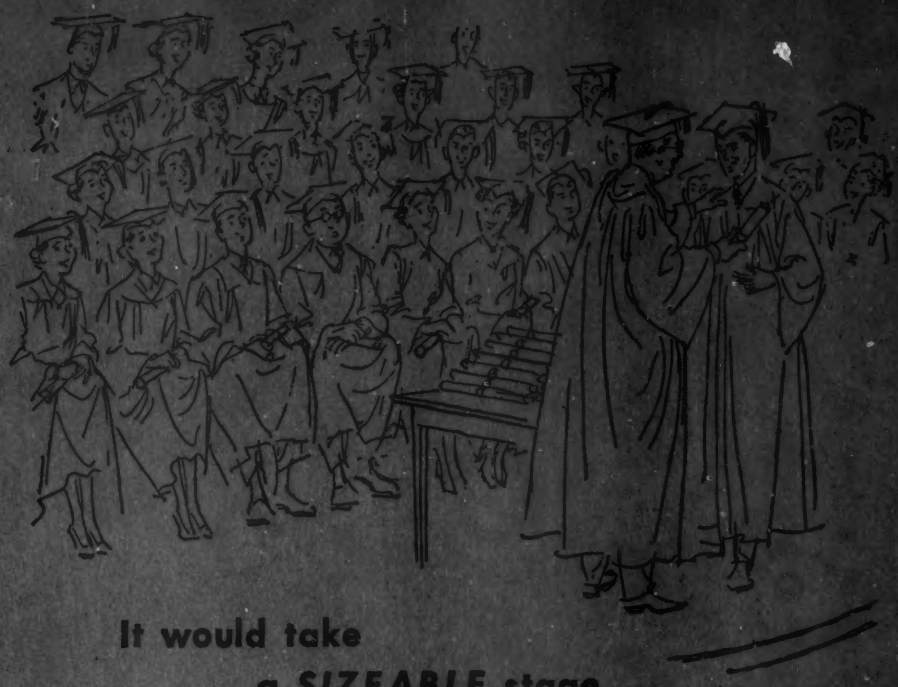

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